Magnetic resonance imaging (MRI) and MRI-targeted biopsy of the prostate

The role of direct in-bore and MRI-ultrasound fusion guided biopsy

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Introduction

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Venderink W, Jenniskens SFM, Fütterer JJ and Sedelaar JPM

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Chapter 12 Reading and reporting standards: The Prostate Imaging Reporting and Data System - What Is It and What Can It Do
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Venderink W and Fütterer JJ

Introduction

In Europe and the United States of America, prostate cancer (PCa) is the most common diagnosed form of cancer among males.[1] Approximately, one out of six men will be diagnosed with the disease. Luckily, the majority of men with PCa will not die from the disease, instead, they die with the disease.[2] The reason is that most men with prostate cancer have low-risk localized PCa. As these low-grade, small-volume and organ-confined PCa lesions are not likely to influence a patient his well-being nor his morbidity, these lesions are often referred to as clinically insignificant PCa. Against this, clinically significant PCa (csPCa) is supposed to affect a man his life.[3] Therefore, the challenge in PCa diagnostics is to accurately identify and detect csPCa without detecting clinically insignificant PCa lesions.

The current standard to diagnose PCa is the pathological examination of prostate tissue obtained with transrectal ultrasound (TRUS) guided biopsies after PSA testing.[4] TRUS biopsy is performed in men with raised prostate specific antigen (PSA) blood levels or in men with an abnormal digital rectal examination (DRE). Systematically, 10-12 biopsy cores are obtained as prostate cancer is often not visible on ultrasound.[5,6] Unfortunately, with the combination of PSA, DRE and TRUS we currently have an inadequate diagnostic work-up for csPCa. A first drawback of TRUS guided biopsy is the over-diagnosis of clinically insignificant PCa. Contrarily, the second drawback is the under-diagnosis of csPCa.[7,8] Often, csPca is missed when using TRUS guided prostate biopsy. Other drawbacks are the underestimation of PCa aggressiveness, the risk of developing sepsis and the use of 10-12 biopsy cores, making it an unpleasant procedure.[9] On the other hand, advantages of TRUS-guided biopsy are the low costs and the ease of use, making the technique readily available to implement.

multiparametric MRI

Since the introduction of multiparametric MRI (mpMRI) and MRI-guided prostate biopsy about a decade ago, there has been a paradigm shift in PCa diagnostics.[10,11] mpMRI is a combination of anatomical and functional MR images that together allow for an accurate assessment of the prostate. To depict the anatomy of the prostate, T2-weighted images are used. The most used functional MR images are diffusion-weighted imaging (DWI) and dynamic contrast-enhanced imaging (DCE).

T2-weighted imaging

T2-weighted imaging is the cornerstone of prostate mpMRI. Due to the high spatial resolution and soft tissue contrast, T2-weighted imaging is ideal for differentiating between the high-signal-intense peripheral zone (PZ) and the low-signal-intense transition zone (TZ) of the prostate. To increase the diagnostic accuracy of

MRI for csPCa, T2-weighted images should be used along with functional imaging techniques.

Diffusion-weighted imaging

In diffusion-weighted imaging (DWI), the Brownian motion of water protons is displayed. Brownian motion is the absolute random motion of water molecules in unrestricted tissue.

DWI consists of two components: high *b*-value images and an apparent diffusion coefficient (ADC). As PCa is highly cellular, it thus restricts water movement which is characterized by a high signal intensity on high *b*-value images.[12]

An ADC map is calculated from at least two *b*-values. An ADC map is an automated calculation process from the MR-scanner. In contrast to high *b*-value images, highly cellular tissue is reflected by a low signal intensity on the ADC map.

Dynamic contrast-enhanced imaging

Dynamic contrast-enhanced imaging (DCE) is an imaging technique representing the vascular properties of tissue. Repeatedly acquired fast T1-weighted sequences before, during and after intravenous administration of a gadolinium-based contrast agent are used in DCE. Dedicated software is needed for post-processing the obtained images. Usually, color maps are extracted from the images for a simple understanding by both radiologists and non-radiologists. The colors used on those maps reflect a specific hemodynamic parameter.[13] Like other cancers, PCa is highly vascularized.

PI-RADS

In 2012 Barentsz *et al.*[14] published the clinical guidelines for mpMRI of the prostate of the European Society of Urogenital Radiology (ESUR). Along with these guidelines, the first version of the Prostate Imaging Reporting and Data System (PI-RADS) classification was introduced (PI-RADS v1). The introduction of PI-RADS v1 allowed radiologists to assess the prostate in a structured manner using a scoring system with predefined requirements that a lesion must satisfy in order to be given a certain level of suspicion for being PCa. However, experience revealed some limitations and therefore there was a need for a new version (PI-RADS v2).[15] Like version 1, PI-RADS v2 is based on a classification ranging from 1 to 5. Lesions are classified based on their appearance on mpMRI. The score predict its chance of being csPCa. The chance of being csPCa, for example, is highly likely in case of a PI-RADS 5 lesion, whereas the chance is likely at PI-RADS 4 and equivocal in PI-RADS 3 lesions.

MRI-targeted biopsy

To date, pathological confirmation of obtained biopsies is still standard to definitively confirm the diagnosis and to assess cancer aggressiveness. Using the detection and localizing ability of mpMRI, it has become possible to perform MRI-targeted biopsy rather than systematically sampling the prostate with TRUS-guided biopsy. Different ways to target suspected lesions are practiced. For example, direct in-bore MR guided biopsy (MRGB) and MRI-TRUS fusion guided biopsy (FGB).

Direct in-bore MR-guided biopsy

Currently, the most commonly used MRGB device is a manually adjustable positioning device for needle guide positioning. A needle guide is inserted in the rectum of the patient. Based on the acquired MR images, the needle guide is manually positioned in the direction of the suspicious lesion. In order to manipulate the direction of the needle guide, the patient has to be withdrawn from the magnet bore and positioned inside the magnet bore again for imaging. Consequently, the physician repeatedly changes between the scanner room and control room to adjust the needle guided direction and interpret the MR images, respectively. Besides the fact that less biopsy cores are needed for diagnosis, this MRGB technique increases the csPCa detection rates in patients.[11] However, MRGB is a time consuming and expensive diagnostic procedure.

MRI-TRUS fusion

In FGB preprocedural achieved mpMRI images are fused with real-time TRUS images. This can be done software assisted or cognitively. In software assisted FGB, mpMRI data has to be loaded onto an ultrasound platform. Software registration combines the advantages of both mpMRI and TRUS by targeting the biopsy needle with real-time TRUS into a previously mpMRI selected lesion. The main difference between the different commercially available FGB platforms is the method of image registration being either rigid or elastic. In elastic image registration, the biopsy platforms tries to compensate for possible deformation of the prostate caused by the introduction of the ultrasound probe. Rigid image registration does not compensate for this prostate deformation.

Current challenges

Nowadays, several routines are being practiced in the diagnostic work up of PCa. Though, there are still some questions to be answered. For example, mpMRI is increasingly being used to detect and localize PCa. Due to a sensitivity of 93% (95% CI, 88-96) and a negative predictive value of 89%, patients without suspicious lesions seen on mpMRI may safely avoid biopsy. Currently, it is not well established which proportion of men avoid such a biopsy in a daily clinical routine. Also, it is not well clarified what proportion of csPCa is detected in mpMRI lesions which are suspicious for harboring csPCa.

Since we are able to localize csPCa, targeted biopsy is used for obtaining tissue for histopathological evaluation. As shown above, there are different ways to target such an mpMRI suspicious lesion. At this moment, it is unclear which targeted biopsy approach is most accurate and most cost-effective. In various ways, these raised questions will be tried to be answered.

Aim and outline of this thesis

The aim of this thesis is to evaluate the role of mpMRI and MRI-targeted prostate biopsy in men with a clinical suspicion of PCa. As different biopsy approaches are being practiced, this thesis further aims to evaluate the role of these different biopsy techniques, especially MRGB and FGB.

Nowadays, mpMRI is increasingly being used to detect and localize PCa. Because of its high sensitivity and negative predictive value, a proportion of patients, those without suspicious lesions, can safely avoid biopsy. In **Chapter 2** we investigated that proportion.

Chapter 3 provides an overview of the detection of (cs)PCa in lesions scored PI-RADS 3, 4 or 5. We evaluated the pathology results after the biopsy of lesions which are classified equivocal, likely or highly likely to be clinically significant on mpMRI. Further, we evaluated in this chapter the ability of the PSA blood level divided by the volume of the prostate (PSA density) to predict csPCa in lesions which are equivocal to be csPCa.

Next, in **Chapter 4,** a retrospective head-to-head comparison between MRGB and FGB is presented. We compared the detection rates for both csPCa and any PCa between both MRI-targeted biopsy techniques.

In **Chapter 5** we evaluated the yield of repeating an MRGB in a suspicious lesion in men who have had a previously MRGB which was negative for PCa in that same lesion.

Currently, the most used MRI-targeted prostate biopsy technique is FGB. Different manufacturers are offering software assisted FGB. As explained earlier, the main difference between the systems is in the way of image registration being either rigid or elastic. Therefore, the aim of **Chapter 6** was to compare rigid and elastic image registration and to compare FGB with 10-12 core systematic TRUS biopsy.

As different biopsy strategies are being practiced nowadays, we evaluated which prostate biopsy technique (systematic TRUS, MRGB or FGB) is most cost-effective. This cost-effectiveness comparison is described in **Chapter 7.**

Finally, in **Chapter 8** the main findings of this thesis are discussed.

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2

Experience in 4259 men to avoid prostate biopsy by using multiparametric MRI and PI-RADS at an expert centre

(submitted)

Venderink W, van Luijtelaar A, van der Leest M, Barentsz JO, Jenniskens SFM, Sedelaar JPM, Hulsbergen - van de Kaa CA, Overduin CG, Futterer JJ

Abstract

Background The limitations of systematic transrectal ultrasound (TRUS) biopsy resulted in increased use of multiparametric (mp)MRI for the diagnostic work up of males suspected of having prostate cancer (PCa). The proportion of males avoiding prostate biopsy in an expert centre is not yet established.

Objective The aim of our study was to determine the proportion of males avoiding biopsy because of negative mpMRI findings in an prostate MRI experienced centre and to determine the amount of clinically significant (cs)PCa detected during follow up in those patients.

Design Prospectively collected data of patients having mpMRI of the prostate in our institution between January 2012 and December 2017 were collected. We included males suspected to have prostate cancer with either a history of negative TRUS biopsy or those who were biopsy naïve. Lesions were classified according to Prostate Imaging Reporting And Data System (PI-RADS) version 1 and 2 by one of our eight radiologists, with varying degree of experience. Institutional review board approval was obtained with a waiver of informed consent.

Outcome Measurements and Statistical Analysis Primary outcome was the proportion of patients with a negative mpMRI, defined as an index lesion classified PI-RADS ≤ 2. Descriptive statistics were used. Histopathologic follow up until 26 March 2018 was collected by searching the Dutch Pathology Registry (PALGA). Gleason score ≥ 3+4 was considered clinically significant (cs)PCa.

Results and limitations A total of 4259 men were included. The median age was 65 years (interquartile range [IQR], 60-70) and median PSA was 8.5 ng/ml (IQR, 6.0-13.0). Patients had a history of prior negative TRUS biopsy in 47.9 % (n = 2039) and were biopsy naïve in 52.1% (n = 2220). In 53.6% (2281/4259) an index lesion was classified PI-RADS ≤ 2. Deciding not to biopsy lesions classified PI-RADS 3 with a PSA density below 0.15 ng/ml/ml would result in an additional 5.8% (total proportion 59.4%) of patients avoiding biopsy.

In 0.4% (9/2281) of the patients with a PI-RADS 1 or 2 classification, csPCa was detected after a median period of 29 months (IQR, 16-49).

Conclusions More than half of patients having mpMRI of the prostate avoided biopsy because of negative findings on mpMRI. Follow up rarely results in csPCa.

Introduction

The current standard of care in men suspected of having prostate cancer (PCa) is a systematic 10-12 core transrectal ultrasound (TRUS) biopsy.[1] However, this technique is limited as clinically significant (cs)PCa is often missed, clinically insignificant cancers are unnecessarily detected and men undergo biopsy while they do not have PCa. In the past few years, evidence accumulated to reduce the above mentioned limitations of TRUS biopsy by using multiparametric (mp)MRI. As a consequence, mpMRI is now increasingly being used to detect and localize csPCa. The opportunity to adequately localize csPCa allows mpMRI to direct the biopsy needle towards a mpMRI suspicious lesion. By using mpMRI and subsequent MRI targeted biopsy, in a proportion of men biopsy may be avoided. Also, mpMRI reduces the over-diagnosis of clinically insignificant PCa.[2,3] Recently, the PROMIS trial reported that 27% of patients may safely avoid biopsy by using mpMRI as triage test.[4] In addition, the PRECISION trial reported similar results.[5] It has been shown that in a well performed mpMRI, patients with negative findings can safely avoid biopsy because of its high sensitivity and negative predictive value (NPV).[4,6,7] However, recent publications showed differences in biopsy thresholds. For example, in our institution men with lesions classified 1 or 2 according to the Prostate Imaging Reporting And Data System version 2 (PI-RADS)[8] and a low clinical suspicion of csPCa do not undergo biopsy, while in other institutes men with lesions classified PI-RADS ≥ 2 undergo biopsy.[9-12] Moreover, recently, the concept of using PSA density (PSAD) in combination with PI-RADS is also being suggested as additional risk tool for csPCa, that can be used to select men who may avoid targeted biopsy in PI-RADS 3 lesions.[11,13,14]

Current results regarding patients avoiding biopsy are largely based on prospective trials in which often double reading is performed or in which multiple, often less experienced, institutions are involved, and not always using 3T MR-scanners. Also, there is limited literature regarding follow-up in patients with negative mpMRI findings.

Therefore, the purpose of our study was to determine the percentage of men who avoided prostate biopsy by using mpMRI in an expert centre and to assess the number of clinically significant (cs)PCa detected during follow-up in these patients.

Material and Methods

Prospectively acquired data from consecutive patients having their first mpMRI of the prostate in our institution between January 2012 and December 2017 were retrospectively collected from our Picture Archiving and Communication System (PACS). Institutional review board approval was obtained with a waiver of informed consent. Included patients had a clinical suspicion for PCa with either a history of negative TRUS biopsy or were biopsy naïve. Patients with biopsy proven PCa and patients with a prior mpMRI of the prostate were excluded from this study. Included patients did not participate in trials within our institution.

Multiparametric MRI

All mpMRI images were obtained using a 3.0 T MR scanner (Skyra; Siemens) with a pelvic phased-array coil. Triplanar T2-weighted images, axial diffusion weighted images and axial dynamic contrast enhancement series were obtained according to the PI-RADS v1 or v2 criteria.8,15 Since 2012 mpMRI parameters are slightly adjusted. However, it met PI-RADS criteria. Images were classified according to the risk assessment either from PIRADS v1 or v2 by one of eight radiologists, who were in-house trained in prostate MR reading (2-20 years of experience). For this study, only the index lesions were used, as this lesion determined whether biopsy was needed. Most recent PSA prior to the mpMRI was collected. Next to the PI-RADS classification, radiologists reported the MRI-PSA density (mPSAD), which is calculated by dividing PSA by the prostate volume on mpMRI.

Data analysis

Descriptive statistics were used for both patient and mpMRI characteristics. The main objective of this study was to determine the amount of men who avoided biopsy. Subgroup analysis was performed for patients with a PI-RADS 3 classification to further evaluate the proportion of patients avoiding biopsy by the addition of different mPSAD threshold next to the PI-RADS classification. Analyses were performed using SPSS software (version 22; IBM). Follow-up until 26 March 2018 was collected using the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA).[16] The follow-up data consisted of histopathology obtained by either TRUS or targeted biopsy. Gleason score ≥ 3+4 was considered clinically significant (cs)PCa.

Results

We included 4259 patients. These patients had a history of prior negative TRUS biopsy in 47.9 % (n = 2039) and were biopsy naïve in 52.1% (n = 2220). The median age was 65 years (interquartile range [IQR], 60-70) and median PSA was 8.5 ng/ml (IQR, 6.0-13.0). An overview of patient characteristics is listed in Table 1.

Table 1 Patient characteristics

Age, yr, median (IQR)	65 (60-70)
Prior TRUS biopsy, n (%)	2039 (47.9)
Biopsy naïve, n (%)	2220 (52.1)
PSA (ng/ml), median (IQR)	8.5 (6.0-13.0)
Prostate volume (ml), median (IQR)	64.0 (46.0-92.0)
PSAD (ng/ml/ml), median (IQR)	0.13 (0.09-0.20)
Year in which mpMRI is performed, n (%)	
2012	665 (15.6)
2013	573 (13.5)
2014	521 (12.2)
2015	808 (19.0)
2016	785 (18.4)
2017	907 (21.3)

IQR = inter quartile range; mpMRI = multiparametric MRI; PI-RADS = Prostate Imaging Reporting And Data System; PSA = prostate specific antigen; PSAD = PSA density; TRUS = Transrectal ultrasound

PI-RADS

Overall, in 53.6% (2281/4259) the index lesion was classified PI-RADS ≤ 2. Thus, 46.4% (1978/4259) needed targeted biopsy because of a PI-RADS 3-5 index lesion (Figure 1). Within the patients with prior negative TRUS biopsy and within the biopsy naïve patients, 52.7% (1075/2039) and 54.3% (1206/2220) were classified PI-RADS ≤ 2 respectively. In the entire cohort, in 11.7% (499/4259) the radiologists classified a lesion PI-RADS 3, which was 14.5% (296/2039) and 9.1% (203/2220) in patients with prior negative TRUS biopsy and in biopsy naïve patients respectively. Table 2 shows the distribution of PI-RADS of the entire cohort.

Differences in patient characteristics between the radiologists are presented in supplementary 1. The proportion of lesions classified PI-RADS ≤ 2 varied from 42.9% (176/410, radiologist 7) to 64.2% (174/271, radiologist 6). The difference in distribution over the years was even smaller, as is shown in Figure 2.

Figure 1 Distribution of PI-RADS scored in the entire cohort

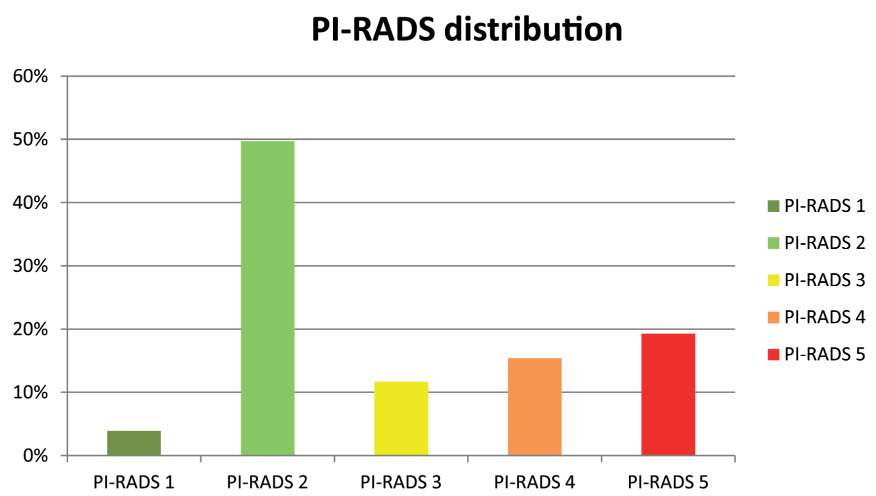


Table 2 PI-RADS distribution of the entire cohort

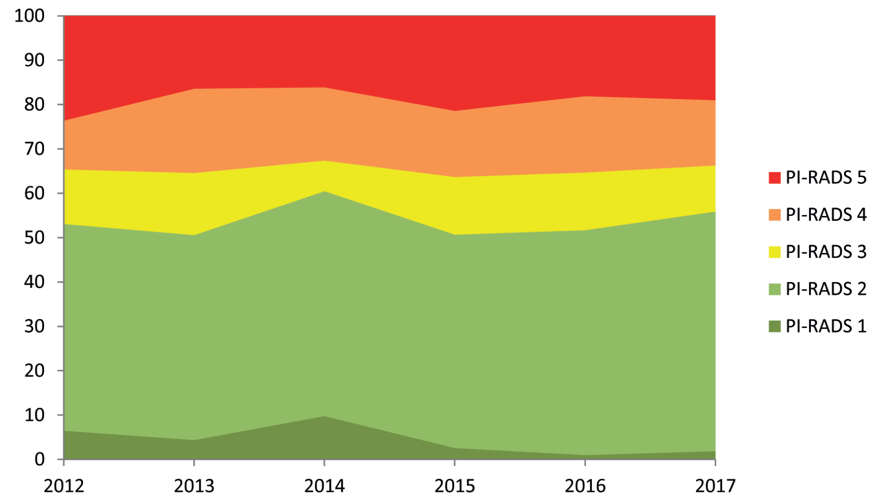
PI-RADS	n	%	Cu %
1	165	3.9	3.9
2	2116	49.7	53.6
3	499	11.7	65.3
4	656	15.4	80.7
5	823	19.3	100.0
Total	4259	100.0	100.0

Cu % = Cumulative percentage; PI-RADS = Prostate Imaging Reporting And Data System

PSA density in PI-RADS 3

In the entire cohort, 57.2% (2435/4259) of the patients had an index lesion classified PI-RADS ≤ 2 or PI-RADS 3 with a mPSAD below 0.12 ng/ml/ml, in these patients biopsy could have been avoided.11 This increases to 58.8% (2506/4259) if the threshold were to be shifted to a mPSAD of 0.15 ng/ml/ml in patients with a PI-RADS 3 index lesion. The distribution of mPSAD in the cohort of 499 patients with a PI-RADS 3 is specified in Table 3.

Figure 2 Distribution of PI-RADS displayed per year



PI-RADS = Prostate Imaging Reporting And Data System.

Follow-up

After a median of 31 months (IQR, 18-52), 3.2% (74/2281) of the patients with PI-RADS ≤ 2 had a follow-up examination of the prostate reported in the nationwide network and registry of histo- and cytopathology in the Netherlands. For PI-RADS 3 this was 28.9% (144/499).

In these 74 patients with PI-RADS ≤ 2, follow-up was acquired after a median of 9 months (IQR, 2-23). Follow-up consisted of TRUS biopsy in 42 patients and targeted biopsy in 32 patients. Within the entire cohort of patients with PI-RADS 1 and 2, PCa was detected in 1.1% (25/2281) and csPca was detected in 0.4% (8/2281). Specified for the cohort of 74 patients with follow-up, csPCa was detected in 10.8% (8/74). CsPCa was detected with TRUS biopsy and with targeted biopsy both 4 times.

In the 144 of the 499 patients with PI-RADS 3, follow-up was obtained after a median of 40 days (IQR, 25-114). TRUS biopsy was done in 9 patients and targeted biopsy in 135 patients. Follow-up was negative in 92 patients. Any PCa was detected in 52 patients, and csPCa was detected in 26 patients. CsPCa was solely detected with targeted biopsy.

Supplementary table 1 Patient characteristics per radiologist

Characteristics	**Radiologist**							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Years of experience	20	12	5	5	5	5	10	2
Total mpMRI studies, n (%)	820 (19.3)	567 (13.3)	1128 (26.5)	724 (17.0)	289 (6.8)	271 (6.4)	410 (9.6)	50 (1.2)
Age, median (IQR)	65 (60- 69)	65 (60-70)	66 (60-70)	65 (60-70)	66 (61-70)	66 (60-70)	65 (60-69)	64 (59-69)
PSA, median (IQR)	9.0 (6.4-14.0)	9.1 (6.2-15.0)	7.5 (5.4-11.0)	8.9 (6.3-13.1)	8.7 (6.2-12.0)	6.8 (5.0-9.0)	10.0 (7.0-16.0)	11.5 (7.8-16.3)
Prior TRUS biopsy, n (%)	483 (58.9)	291 (51.3)	395 (35.0)	368 (50.8)	146 (50.5)	53 (19.6)	266 (64.9)	36 (72.0)
Biosy naïve, n (%)	337 (41.1)	276 (48.7)	733 (65.0)	356 (49.2)	143 (49.5)	218 (80.4)	144 (35.1)	14 (28.0)
PSA density, median (IQR)	0.14 (0.09-0.21)	0.14 (0.09-0.22)	0.11 (0.08-0.16)	0.14 (0.09-0.23)	0.12 (0.09-0.20)	0.10 (0.07-0.15)	0.16 (0.11-0.26)	0.22 (0.13-0.32)
PI-RADS, n (%)								
1	60 (7.3)	19 (3.4)	72 (6.4)	5 (0.7)	3 (1.0)	2 (0.7)	1 (0.2)	3 (6.0)
2	377 (46.0)	273 (48.1)	584 (51.8)	387 (53.5)	127 (43.9)	172 (63.5)	175 (42.7)	21 (42.0)
3	108 (13.2)	66 (11.6)	87 (7.7)	97 (13.4)	47 (16.3)	6 (2.2)	79 (19.3)	9 (18.0)
4	94 (11.5)	114 (20.1)	183 (16.2)	104 (14.4)	55 (19.0)	49 (18.1)	49 (12.0)	8 (16.0)
5	181 (22.1)	95 (16.8)	202 (17.9)	131 (18.1)	57 (19.7)	42 (15.5)	106 (25.9)	9 (18.0)

IQR = inter quartile range; mpMRI = multiparametric MRI; PI-RADS = Prostate Imaging Reporting And Data System; PSA = prostate specific antigen; PSAD = PSA density; TRUS = Transrectal ultrasound

Table 3 Distribution of PSAD in 499 patients with PI-RADS 3

PSAD (ng/ml/ml)	**n (499)**	**%**	**Cu %**
≤ 0.1	123	24.6	24.6
0.11	31	6.2	30.9
0.12	21	4.2	35.1
0.13	29	5.8	40.9
0.14	21	4.2	45.1
0.15	22	4.4	49.5
≥0.16	252	50.5	100

Cu % = Cumulative percentage ; PI-RADS = Prostate Imaging Reporting And Data System; PSAD = Prostate Specific Antigen Density

There was follow-up in 49 of the 154 patients with a mPSAD below 0.12 ng/ml/ml. Eight of them had csPCa (0.4%). There was follow-up in 63 of 225 patients with a mPSAD below 0.15 ng/ml/ml. In 13 of these patients csPCa was found.

A csPCa was found in 0.7% (16/2435) for PI-RADS 1-2 plus PI-RADS 3 with a mPSAD <0.12ng/ml/ml and in 0.8% (21/2506) for PI-RADS 1-2 plus PI-RADS 3 with a mPSAD <0.15ng/ml/ml.

Discussion

The primary finding of our study is that 53.6% of patients had a negative mpMRI (PI-RADS ≤ 2) and avoided biopsy in our institution. An additional 5.2% could avoid biopsy in PI-RADS 3 lesions with a mPSAD below 0.15 ng/ml/ml. Our follow-up data shows that a negative mpMRI is reassuring to patients and urologists as in only 3.2% further TRUS or targeted biopsy was obtained after a median of 31 months. A clinically significant PCa was found only in 0.4% for PI-RADS 1-2 and 0.7% for PI-RADS 1-2 plus PI-RADS 3 with a mPSAD <0.12ng/ml/ml.

Our results are the first to report on such a large cohort of patients with a clinical suspicion of csPCa having an mpMRI in an clinical setting atan expert setting. The finding that in clinical practice more than 50% of patients who have a negative mpMIR may avoid biopsy, underlines the importance of mpMRI in the diagnostic work up of csPCa. By avoiding additional biopsy, costs and post-biopsy complications can be reduced.[17-19]

Compared to the findings of the PROMIS trial as well as the findings of the PRECISION trial, our number of patients who could avoid biopsy are approximately twice as high.[4,5] Next to these trials, also other groups presented results remarkably differing from the results presented in this paper. In those studies, the cohort classified PI-RADS 1-2 varied from 11% to 38%.[12,20-22] An explanation is that PI-RADS may be applied conservatively in the afore mentioned studies with a prospective study design, so as not to miss any significant tumors. This may introduce a bias, which is not present in the routinely scored exams of this retrospective study. Furthermore, our institution is very experienced in prostate MRI reading, which is reflected in the low number of patients classified PI-RADS 3 (12%). This is low, for example, compared to the PROMIS trial (28%) or the PRECISION trial (20%). A PI-RADS 3 classification implies an uncertainty either due to the quality of the images or to the expertise of the radiologist or due to the patient population.

Another explanation may be that a part of our patients with a PI-RADS 1 or 2 was false negative. However, our follow-up demonstrates that csPCa was rarely detected in patients with a negative mpMRI (0.4%). Therefore, it is unlikely that this is the explanation for the relatively large proportion of patients with PI-RADS ≤ 2.

In the recently published PRECISION trial, Kasivisvanathan et al. raised their concerns about men with negative results on mpMRI who do not undergo biopsy.[5] They referred to the PROMIS trial that showed that men with negative mpMRI findings have a low risk of csPCa (5%). In addition, the PRECISION trial demonstrated that negative mpMRI findings were more reassuring for patients and urologists than a negative result on TRUS biopsy. Our results confirm these findings by demonstrating that in a daily clinical setting only 3.2% of men with negative mpMRI findings requests additional TRUS or targeted biopsy and in only 0.4% csPCa was detected. In patients with equivocal findings (PI-RADS 3), a much larger group requests additional targeted biopsy (28.9%).

The most important strength of our study, is the large cohort of patients having a PI-RADS standardized mpMRI acquisition and reporting at a prostate MR expert centre. As the first patients included in our study had an mpMRI in 2012 already, we explored the differences in PI-RADS distribution over the years. We demonstrated that scoring distribution did not differ notably.

Despite the afore mentioned strengths, there are also several limitations. First, there is a lack of direct pathological confirmation after negative mpMRI results. It would be ideal to have a gold standard, for example template biopsy mapping, in all these men with negative mpMRI findings to ensure there is no csPca. Of course, this is not possible in a daily clinical setting. Therefore, follow-up data was obtained from PALGA. PALGA is a nationwide network and registry of histo- and cytopathology in the Netherlands. In this database, every histo- and cytopathology obtained in our country is stored. As a consequence, presented follow-up only consists of pathology obtained by TRUS or targeted biopsy. Follow-up concerning digital rectal examination, PSA or other biomarkers and mpMRI is not

included in this paper. Therefore, follow-up was only available in a small amount of included patients. However, PALGA stores every pathology outcome in our country. As a consequence, in none of the patients without follow-up, there was PCa detected anywhere in the Netherlands. Therefore, with a median follow-up of 31 months, it is not likely that highly aggressive PCa's will be missed in patients with PI-RADS 1-2.

Furthermore, several other studies have already investigated the NPV of mpMRI and concluded that patients with negative mpMRI results may safely avoid prostate biopsy.23-26 In a previous study we already reported biopsy outcome in patients with PI-RADS ≥ 3.[11]

As our study aimed to address the question which proportion of patients may avoid biopsy based on the current practice, the lack of direct pathological confirmation does not influence our conclusion.

A second limitation is that results presented in this paper may be hard to extrapolate and only be applicable for a highly experienced prostate mpMRI center and could not be generalized as our institution is very experienced in acquisition and reading of mpMRI images. Due to weekly multidisciplinary biopsy meetings where pathology, MRI and targeted biopsy are discussed we established a steep learning curve. An advantage is that we demonstrated the potential of mpMRI if assessed by well-trained radiologists due to regular pathology feedback.

Conclusions

In our large patient cohort (4259), mpMRI was classified negative of having csPCa in more than half of patients (53.6%). As a consequence, they may safely avoid biopsy and the subsequent inconveniences, risks and costs associated. Furthermore, a negative mpMRI is reassuring to patients and urologists as in only a few percent (3.2%) further TRUS or targeted biopsy was required, and csPCa's (0.4%) were detected.

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3

Results of targeted biopsy in men with magnetic resonance imaging lesions classified equivocal, likely or highly likely to be clinically significant prostate cancer

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Abstract

Background The Prostate Imaging Reporting And Data System (PI-RADS) is the most commonly used scoring system in prostate MRI. One of the available techniques to target suspicious lesions is direct in-bore MRI-guided biopsy (MRGB).

Objective To report on the experience and results of MRGB in a large cohort of patients with lesions classified as equivocal (PI-RADS 3), likely (PI-RADS 4) or highly likely (PI-RADS 5) to be clinically significant (cs) prostate cancer (PCa).

Design, Setting and Participants We retrospectively included 1057 patients having MRGB, between January 2012 and September 2016, of lesions classified PI-RADS ≥ 3 on mpMRI. Biopsy-naïve patients, patients with prior negative systematic transrectal ultrasound-guided (TRUS) biopsy and patients in active surveillance were included.

Outcome Measurements and Statistical Analysis The primary outcome measurement is the detection rate of (cs)PCa. Descriptive statistics and chi-squared tests were used to calculate for differences in proportions. We considered a Gleason score ≥ 3+4 being csPCa.

Results and limitations PCa was diagnosed in 35% (55/156), 60% (223/373) and 91% (479/528) in patients with PI-RADS 3, 4 and 5 respectively and csPCa in 17% (26/156), 34% (128/373) and 67% (352/528) respectively. Follow up of patients with negative biopsy findings resulted in csPCa in 1.7% (5/300) after a median period of 41 (IQR 25-50) months. The evaluation of prostate specific antigen density (PSAD) to predict csPCa resulted in 42% of patients with a PI-RADS3 that could avoid biopsy in case a PSAD of ≥ 0.15 ng/mL/mL would be used. In 6% (95% CI, 2-15) a csPCa would then be missed. The study is limited because of its retrospective character.

Conclusion MRGB in lesions scored PI-RADS ≥ 3 yields high detection rates of csPCa. in daily clinical practice in previous negative biopsy cases.

Introduction

The role of magnetic resonance imaging (MRI) in the detection and localization of prostate cancer (PCa) rose after the introduction of multiple functional MRI parameters that were added to anatomical MRI approximately a decade ago.[1-3] Despite the high performance of this multiparametric (mp)MRI, systematic 10-12 core transrectal ultrasound (TRUS) guided prostate biopsy is still the standard used to detect PCa.[4]

To improve the diagnostic quality of prostate mpMRI and to simplify and standardize radiology reports, the European Society of Urogenital Radiology introduced in 2012 the first version of the Prostate Imaging Reporting And Data System (PI-RADS v1).[5] Very recently, a new version (PI-RADS v2) was introduced.[6] Both version 1 and version 2 of PI-RADS are scoring systems based on a 5-point Likert scale. Following the imaging characteristics of a lesion on the different MRI parameters, an overall score is given to a lesion to predict its chance of being clinically significant (cs) PCa. The chance of being csPCa, for example, is highly likely in case a PI-RADS score of 5 is given whereas the chance is likely at a score of 4 and equivocal in PI-RADS 3 lesions.

After a PI-RADS assessment category is assigned to a lesion, the lesion has to be biopsied on a targeted way to confirm the diagnosis. One way to target such a lesion is by performing direct in-bore MRI guided biopsy (MRGB).

Despite much research in PI-RADS classification and different prostate biopsy approaches, a broad evaluation of the implication of PI-RADS in large cohorts of patients who have undergone MRGB is not performed yet. Therefore, the main aim of our study is to outline MRI-guided biopsy findings in patients with differing levels of suspicion at mpMRI and to demonstrate follow up of patients with negative biopsy findings despite a positive mpMRI. Further we will examine the ability of prostate specific antigen density (PSAD) to predict biopsy outcome, the implication location has on PCa detection and the meaning of detecting lesions next to the index lesion.

We will address those issues based on our MRGB results since 2012 in men with lesions classified PI-RADS 3, 4 and 5.

Patients and Methods

This retrospective study with prospectively collected data was approved by our institutional review board with a waiver of written informed consent (2016-2739).

Patients

All patients having MRGB and prior mpMRI in our institution between January 2012 and September 2016 were identified. Patients with prior targeted biopsy, prior treatment of the prostate or with biopsy proven PCa ≥ 3+4 Gleason score (GS) were excluded from our study (fig. 1). Patients included in this study did not participate in other trials of our institution.

Multiparametric MRI

Multiparemetric MRI was performed on a 3.0 T MR-scanner (Siemens, Skyra) with a pelvic phased-array coil. Owing to the large time span in which patients were included, there is a slight variation in mpMRI technical specifications, although it always met the PI-RADS criteria.

Multiparametric MRI images were interpreted by six radiologists with a varying range of experience in prostate MR reading (2-20 years). All images were scored according to PI-RADs v1 or v2. In all patients, next to the PI-RADS score, PSAD is also measured. PSAD is calculated by dividing PSA blood level by the volume of the prostate; hereby, high PSA blood levels, for example, are corrected for large prostate volumes.

MRI-guided biopsy

During MRGB, performed in a separate session, patients were placed in the prone position with an MR compatible needle guide rectally inserted, attached to a biopsy device (Dynatrim, Invivo). Additional axial T2W and axial diffusion-weighted image were obtained to reproduce the location of the lesion. The needle guide was manually positioned using true fast imaging with steady-state free precession (TRUFI) images. Biopsy cores were obtained with an MR-compatible 18-gauge automatic biopsy gun. The position of the biopsy needle was confirmed with TRUFI images which were evaluated by one of the prostate MR experienced radiologists. We only performed targeted biopsy without additional random biopsy. Obtained pathological tissue was interpreted by dedicated uropathologists.

Data analysis

Patients were divided into cohorts based on their biopsy history (biopsy naïve, prior negative TRUS biopsy or in active surveillance (AS)). Descriptive statistics were used to present patient characteristics and detection rates within these different cohorts. We considered a Gleason score ≥ 3+4 being csPCa. Chi-square tests were used to calculate for differences in proportions. In patients with multiple lesions, an index lesion was determined according to PI-RADS. The index lesion is the one with the highest PI-RADS score. If an equal PI-RADS score is assigned to two or more lesions, the index lesion is the one that shows extra prostatic extension (EPE). If none of the lesions demonstrate EPE, the largest tumor is considered the index lesion.[5, 6] Analyses were performed with SPSS software (version 22, IBM).

Follow up

Follow up until October 17, 2016 of patients with a negative MRGB result was obtained by reviewing our nationwide network and registry of histo- and cytopathology (PALGA). Prostate histology obtained by targeted or TRUS biopsy, transurethral resection of the prostate (TURP) or open prostatectomy were evaluated.

Results

After exclusion, 1057 patients left for analysis. Overall, 184 patients were biopsy naïve, 649 had a history of prior negative TRUS biopsy and 224 were on active surveillance with a GS 3+3. PI-RADS 3, 4 or 5 lesions were found in 156, 373 and 528 patients respectively. A total of 1393 lesions were biopsied. Full patient characteristics are presented in table 1.

Biopsy results

PCa was detected in 72% (757/1057) of all patients. Biopsy in patients with PI-RADS 3, 4 and 5 lesions resulted in PCa in 35% (55/156), 60% (223/373) and 91% (479/528) and resulted in csPCa in 17% (26/156), 34% (128/373) and 67% (352/528) respectively. In 67% (506/757) of all detected PCa and in 48% (506/1057) of all included patients, csPCa was detected. The csPCa detection rate was 50% (92/184) for patients without previous TRUS biopsy, 49% (319/649) for patients with prior negative TRUS biopsy and 42% (95/224) for patients in AS. In table 2, detailed PCa findings are listed.

In table 3 biopsy pathology other than PCa is specified. Biopsy did not result in any pathology in 37.2%, 19.8% and 4.4% in PI-RADS 3, 4 and 5. Most commonly prostatitis is diagnosed next to PCa (9%).

Follow up

After a median period of 41 (IQR 25-50) months, 82 of 300 patients without PCa at MRGB had follow up histology of the prostate. Targeted biopsy was performed in 49, TRUS biopsy in 14, TURP in 13 and open prostatectomy in 6 patients. Overall, in 1.7% (5/300) of all patients without PCa detected at biopsy, csPCa was found during follow up. In table 4, findings during follow up are specified.

Table 1 Patient characteristics

	All patients (n = 1057)	Biopsy naïve (n = 184)	Prior negative TRUS (n = 649)	Active Surveillance (n = 224)
Age, yr, median (IQR)	66 (61-69)	66 (61-70)	66 (61-66)	65 (60-69)
PSA level, ng/ml, median (IQR)	10.4 (7.1-16.7)	8.3 (5.9-15.0)	12.0 (8.5-18.1)	7.8 (5.7-11.0)
Prostate volume, ml, median (IQR)	53 (37-73)	46 (33-64)	57 (41-80)	48 (36-62)
PSA density, ng/ml/ml, median (IQR)	0.19 (0.13-0.32)	0.18 (0.12-0.31)	0.21 (0.14-0.36)	0.17 (0.11-0.23)
PI-RADS score, % (n)				
3	14.8 (156)	9.2 (17)	16.3 (106)	14.7 (33)
4	35.3 (373)	36.4 (67)	35.1 (228)	34.8 (78)
5	50.0 (528)	54.3 (100)	48.5 (315)	50.4 (113)
PI-RADS version, % (n)				
1	80.1 (847)	80.4 (148)	81.2 (527)	76.8 (172)
2	19.9 (210)	19.6 (36)	18.8 (122)	23.2 (52)
Target lesions, % (n)	100 (1393)	16.4 (229)	62.6 (872)	21.0 (292)
Men with 1 target, % (n)	71.8 (759)	78.8 (145)	69.5 (451)	72.8 (163)
Men with 2 targets, % (n)	24.6 (260)	17.9 (33)	26.7 (173)	24.1 (54)
Men with 3 targets, % (n)	3.6 (38)	3.3 (6)	3.9 (25)	3.1 (7)
Time between MRI and MRGB, days, median (IQR)	37 (22-56)	37 (20-57)	39 (23-56)	34.5 (21-55)
Biopsies per lesion, n, median (IQR)	2 (2-3)	2 (2-3)	2 (2-3)	2 (2-3)

TRUS = transrectal ultrasound guided biopsy; yr = year; IQR = inter quartile range; PSA = prostate specific antigen; PI-RADS = Prostate Imaging Reporting And Data System; MRI = magnetic resonance imaging; MRGB = MRI guided biopsy.

Table 2 Prostate cancer detection

	All patients (n = 1057)	Biopsy naïve (n = 184)	Prior negative TRUS (n = 649)	Active Surveillance (n = 224)
PI-RADS 3, % (n)	14.8 (156)	9.2 (17)	16.3 (106)	14.7 (33)
No PCa	64.7 (101)	47.1 (8)	73.6 (78)	45.5 (15)
≤ 3+3	18.6 (29)	35.3 (6)	7.5 (8)	45.5 (15)
2+4	-	-	-	-
3+4	9.0 (14)	-	10.4 (11)	9.1 (3)
2+5	-	-	-	-
4+3	5.1 (8)	11.8 (2)	5.7 (6)	-
4+4	1.3 (2)	5.9 (1)	0.9 (1)	-
3+5	0.6 (1)	-	0.9 (1)	-
5+3	-	-	-	-
4+5	0.6 (1)	-	0.9 (1)	-
5+4	-	-	-	-
5+5	-	-	-	-
PI-RADS 4, % (n)	35.3 (373)	36.4 (67)	35.1 (228)	34.8 (78)
No PCa	40.2 (150)	38.8 (26)	44.3 (101)	29.5 (23)
≤ 3+3	25.2 (94)	29.9 (20)	20.6 (47)	34.6 (27)
2+4	0.3 (1)	1.5 (1)	-	-
3+4	22.2 (83)	20.9 (14)	21.5 (49)	25.6 (20)
2+5	-	-	-	-
4+3	5.9 (22)	6.0 (4)	5.7 (13)	6.4 (5)
4+4	2.7 (10)	1.5 (1)	3.9 (9)	-
3+5	1.3 (5)	1.5 (1)	1.3 (3)	1.3 (1)
5+3	-	-	-	-
4+5	1.3 (5)	-	1.3 (3)	2.6 (2)
5+4	0.8 (3)	-	1.3 (3)	-
5+5	-	-	-	-
PI-RADS 5, % (n)	50.0 (528)	54.3 (100)	48.5 (315)	50.4 (113)
No PCa	9.3 (49)	9.0 (9)	9.8 (31)	8.0 (9)
≤ 3+3	23.9 (126)	22.0 (22)	20.3 (64)	35.4 (40)
2+4	0.2 (1)	-	0.3 (1)	-
3+4	29.7 (157)	28.0 (28)	30.8 (97)	28.3 (32)
2+5	0.2 (1)	-	0.3 (1)	-
4+3	15.7 (83)	22.0 (22)	15.9 (50)	9.7 (11)
4+4	10.0 (53)	8.0 (8)	11.1 (35)	8.8 (10)
3+5	2.8 (15)	2.0 (2)	2.2 (7)	5.3 (6)
5+3	0.8 (4)	-	1.3 (4)	-
4+5	5.9 (31)	5.0 (5)	7.0 (22)	3.5 (4)
5+4	1.3 (7)	4.0 (4)	0.6 (2)	0.9 (1)
5+5	0.2 (1)	-	0.3 (1)	-

TRUS = transrectal ultrasound guided biopsy; PI-RADS = Prostate Imaging Reporting And Data System; PCa = prostate cancer

Table 3 Pathology findings in 300 patients without detected prostate cancer

	PI-RADS 3, % (n)	PI-RADS 4, % (n)	PI-RADS 5, % (n)
Prostatitis	15.4 (24)	14.5 (54)	3.2 (17)
High grade PIN	5.8 (9)	1.9 (7)	0.4 (2)
Granulomatous inflammation	1.3 (2)	1.1 (4)	0.6 (3)
Atrophia	3.8 (6)	2.4 (9)	0.6 (3)
Atypical adenomatous hyperplasia	1.3 (2)	0.5 (2)	0.2 (1)
No pathology	37.2 (58)	19.8 (74)	4.4 (23)

PI-RADS = Prostate Imaging Reporting And Data System; PIN = prostatic intraepithelial neoplasia.

Table 4 Follow up of 300 patients without detected prostate cancer

	No PCa	GS 3+3	GS ≥ 3+4	No follow up
PI-RADS 3, % (n)	17.8 (18)	5.9 (6)	1.0 (1)	75.2 (76)
PI-RADS 4	22.7 (34)	3.3 (5)	2.0 (3)	72.0 (108)
PI-RADS 5	20.4 (10)	8.2 (4)	2.0 (1)	69.4 (34)
Total	20.7 (62)	5.0 (15)	1.7 (5)	72.7 (218)

PCa = prostate cancer; GS = Gleason score; PI-RADS = Prostate Imaging Reporting And Data System

PSAD to predict csPCa

For each PI-RADS classification (PI-RADS 3,4 and 5) we examined the ability of different PSAD cutoff levels ranging from 0.1 to 0.25 to predict csPCa after initial biopsy (Supplementary table 1).

Biopsying only patients with a PI-RADS 3 and a PSAD ≥ 0.15 ng/ml/ml results in 42% of patients with a PI-RADS 3 who would avoid biopsy. In 6% (95% CI, 2-15) of the patients who avoid biopsy, csPCa would be missed. Lowering the cutoff value to 0.12 ng/ml/ml results in 26% of patients with a PI-RADS 3 avoiding biopsy and in none of them (95% CI, 0-9) csPCa would have been missed (table 5). Applying the same cutoff values in patient with PI-RADS 4 would avoid MRGB in 38% and 25% respectively. In 23% (95% CI, 17-31) and 20% (95% CI, 13-30) csPCa would have been missed, respectively.

Within the cohort of patients with a PI-RADS 5 the percentages of missed csPCa would increase to 52% (95% CI, 43-60) and 45% (95% CI, 33-57) respectively, with these cutoff values.

Table 5 Summary of clinical consequences when applying PSAD cut-off levels ranging from 0.1-0.25 to predict csPCa in patients with PI-RADS 3

	PSAD cut-off (ng/mL/mL)	**≥ 0.1**	**≥ 0.11**	**≥ 0.12**	**≥ 0.13**	**≥ 0.14**	**≥ 0.15**
PI-RADS 3	Patients with PI-RADS 3 that avoid biopsy	19%	21%	26%	32%	37%	42%
	csPCa missed in patients below the cut-off, (95% CI)	0% (0-12)	0% (0-11)	0% (0-9)	4% (1-13)	3% (1-12)	6% (2-15)
	csPCa detection above the cut-off	20% (14-29)	21% (15-29)	22% (16-31)	23% (16-31)	24% (17-34)	24% (17-34)
	PSAD cut-off (ng/mL/mL)	**≥ 0.16**	**≥ 0.17**	**≥ 0.18**	**≥ 0.19**	**≥ 0.2**	
PI-RADS 3	Patients with PI-RADS 3 that avoid biopsy	42%	45%	49%	53%	56%	
	csPCa missed in patients below the cut-off, (95% CI)	8% (3-17)	8% (3-17)	9% (5-18)	9% (4-17)	11% (6-20)	
	csPCa detection above the cut-off	23% (16-33)	23% (16-33)	24% (16-34)	26% (17-37)	24% (15-35)	
	PSAD cut-off (ng/mL/mL)	**≥ 0.21**	**≥ 0.22**	**≥ 0.23**	**≥ 0.24**	**≥ 0.25**	
PI-RADS 3	Patients with PI-RADS 3 that avoid biopsy	60%	64%	68%	70%	71%	
	csPCa missed in patients below the cut-off, (95% CI)	11% (6-18)	11% (6-19)	14% (9-22)	15% (9-23)	15% (10-23)	
	csPCa detection above the cut-off	26% (17-38)	27% (17-40)	22% (13-35)	21% (12-35)	20% (11-34)	

csPCa = clinically significant prostate cancer; PSAD = prostate specific antigen density; PI-RADS = Prostate Imaging Reporting And Data System; GS = Gleason score

Supplementary Table 1 Summary of clinical consequences when applying PSAD cut-off levels ranging from 0.1-0.25 to predict csPCa in patients with PI-RADS 3, 4 and 5

	PSAD cut-off (ng/mL/mL)	≥ 0.1	≥ 0.11	≥ 0.12	≥ 0.13	≥ 0.14	≥ 0.15
PI-RADS 3	Patients with PI-RADS 3 that avoid biopsy	19%	21%	26%	32%	37%	42%
	csPCa missed in patients below the cut-off, (95% CI)	0% (0-12)	0% (0-11)	0% (0-9)	4% (1-13)	3% (1-12)	6% (2-15)
	csPCa detection above the cut-off	20% (14-29)	21% (15-29)	22% (16-31)	23% (16-31)	24% (17-34)	24% (17-34)
	PSAD cut-off (ng/mL/mL)	**≥ 0.16**	**≥ 0.17**	**≥ 0.18**	**≥ 0.19**	**≥ 0.2**	
	Patients with PI-RADS 3 that avoid biopsy	42%	45%	49%	53%	56%	
	csPCa missed in patients below the cut-off, (95% CI)	8% (3-17)	8% (3-17)	9% (5-18)	9% (4-17)	11% (6-20)	
	csPCa detection above the cut-off	23% (16-33)	23% (16-33)	24% (16-34)	26% (17-37)	24% (15-35)	
	PSAD cut-off (ng/mL/mL)	**≥ 0.21**	**≥ 0.22**	**≥ 0.23**	**≥ 0.24**	**≥ 0.25**	
	Patients with PI-RADS 3 that avoid biopsy	60%	64%	68%	70%	71%	
	csPCa missed in patients below the cut-off, (95% CI)	11% (6-18)	11% (6-19)	14% (9-22)	15% (9-23)	15% (10-23)	
	csPCa detection above the cut-off	26% (17-38)	27% (17-40)	22% (13-35)	21% (12-35)	20% (11-34)	

Supplementary Table 1 Continued

	PSAD cut-off (ng/mL/mL)	≥ 0.1	≥ 0.11	≥ 0.12	≥ 0.13	≥ 0.14	≥ 0.15
PI-RADS 4	Patients with PI-RADS 4 that avoid biopsy	17%	22%	25%	31%	34%	38%
	csPCa missed in patients below the cut-off, (95% CI)	17% (10-28)	21% (14-31)	20% (13-30)	19% (13-27)	20% (14-27)	23% (17-31)
	csPCa detection above the cut-off	38% (33-44)	38% (33-44)	39% (34-45)	41% (35-47)	42% (36-48)	41% (35-48)
	PSAD cut-off (ng/mL/mL)	**≥ 0.16**	**≥ 0.17**	**≥ 0.18**	**≥ 0.19**	**≥ 0.2**	
	Patients with PI-RADS 4 that avoid biopsy	42%	44%	49%	53%	57%	
	csPCa missed in patients below the cut-off, (95% CI)	22% (16-29)	22% (16-29)	23% (18-30)	25% (20-32)	25% (20-32)	
	csPCa detection above the cut-off	43% (37-50)	44% (37-51)	45% (38-52)	44% (37-52)	46% (38-54)	
	PSAD cut-off (ng/mL/mL)	**≥ 0.21**	**≥ 0.22**	**≥ 0.23**	**≥ 0.24**	**≥ 0.25**	
	Patients with PI-RADS 4 that avoid biopsy	61%	65%	67%	68%	70%	
	csPCa missed in patients below the cut-off, (95% CI)	26% (21-32)	27% (22-33)	28% (22-33)	28% (23-33)	28% (23-33)	
	csPCa detection above the cut-off	48% (40-56)	47% (39-56)	48% (39-57)	48% (40-57)	50% (41-59)	

Supplementary Table 1 Continued

	PSAD cut-off (ng/mL/mL)	≥ 0.1	≥ 0.11	≥ 0.12	≥ 0.13	≥ 0.14	≥ 0.15
PI-RADS 5	Patients with PI-RADS 5 that avoid biopsy	8%	10%	13%	16%	20%	23%
	csPCa missed in patients below the cut-off, (95% CI)	35% (22-50)	39% (27-52)	45% (33-57)	47% (37-58)	50% (41-60)	52% (43-60)
	csPCa detection above the cut-off	69% (65-73)	70% (66-74)	70% (66-74)	71% (66-75)	71% (66-75)	71% (67-75)
	PSAD cut-off (ng/mL/mL)	**≥ 0.16**	**≥ 0.17**	**≥ 0.18**	**≥ 0.19**	**≥ 0.2**	
	Patients with PI-RADS 5 that avoid biopsy	27%	32%	36%	39%	43%	
	csPCa missed in patients below the cut-off, (95% CI)	52% (44-61)	55% (48-62)	56% (49-63)	56% (49-62)	58% (52-64)	
	csPCa detection above the cut-off	72% (67-76)	72% (67-77)	73% (68-77)	74% (69-78)	73% (68-78)	
	PSAD cut-off (ng/mL/mL)	**≥ 0.21**	**≥ 0.22**	**≥ 0.23**	**≥ 0.24**	**≥ 0.25**	
	Patients with PI-RADS 5 that avoid biopsy	46%	49%	52%	54%	55%	
	csPCa missed in patients below the cut-off, (95% CI)	58% (51-64)	58% (52-64)	58% (52-64)	59% (53-64)	59% (53-65)	
	csPCa detection above the cut-off	74% (69-79)	75% (69-80)	76% (71-81)	76% (71-81)	76% (70-81)	

csPCa = clinically significant prostate cancer; PSAD = prostate specific antigen density; PI-RADS = Prostate Imaging Reporting And Data System; GS = Gleason score

Prostate cancer detection differentiated per location

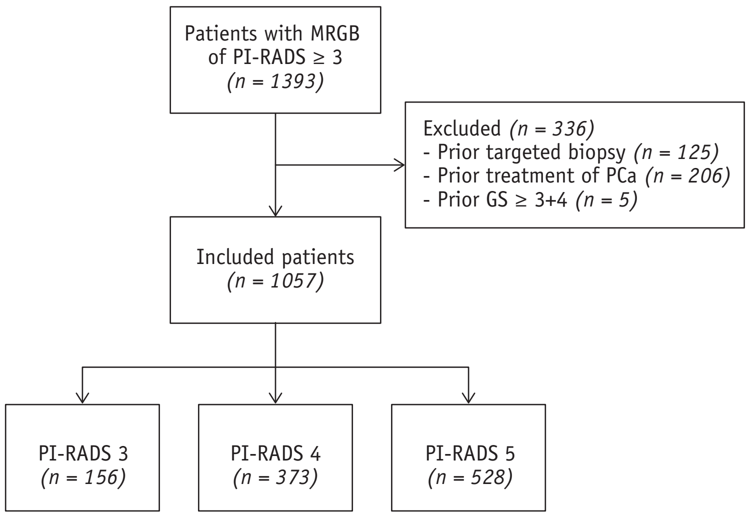
Of all index lesions, 32% (n = 343) was located within the transition zone (TZ), 46% (n = 489) within the peripheral zone (PZ) and 21% (n = 225) of the lesions were overlapping both zones. The csPCa detection rates between the different zones differ significantly from each other ($p < 0.01$) with a detection rate of 52% (n = 177), 41% (n = 198) and 58% (n = 131) respectively. Within the three cohorts, this difference is seen only in patients with prior negative TRUS biopsy ($p < 0.01$) but not in biopsy naïve patients ($p = 0.85$) or in patients in AS ($p = 0.44$) (table 6). The csPCa detection rate within the PZ in men with prior negative TRUS biopsy (35%) is significantly lower compared to the detection rates in the same location in the cohort of biopsy naïve patients (51%, $p < 0.01$) but not in the cohort of patients in AS (42%, $p = 0.17$). In figure 2 and table 7, locations of the lesions are stratified into the following regions: base, midportion and the apex of the prostate.

Table 6 Location of csPCa detection displayed per PI-RADS classification and per cohort

	Transition zone (TZ)	Peripheral zone (PZ)	Overlap TZ and PZ	P value
PI-RADS, % (n)				
3	23 (14/61)	11 (8/72)	17 (4/23)	0.19
4	45 (59/131)	27 (51/189)	34 (18/53)	<0.01
5	69 (104/151)	61 (139/228)	73 (109/149)	0.04
Cohorts, % (n)				
Biopsy naïve	50 (18/36)	51 (56/109)	46 (18/39)	0.85
Prior negative TRUS	55 (139/254)	35 (85/244)	63 (95/151)	<0.01
Active Surveillance	38 (20/53)	42 (57/136)	51 (18/35)	0.44
Total	52 (177/343)	41 (198/489)	58 (131/225)	<0.01

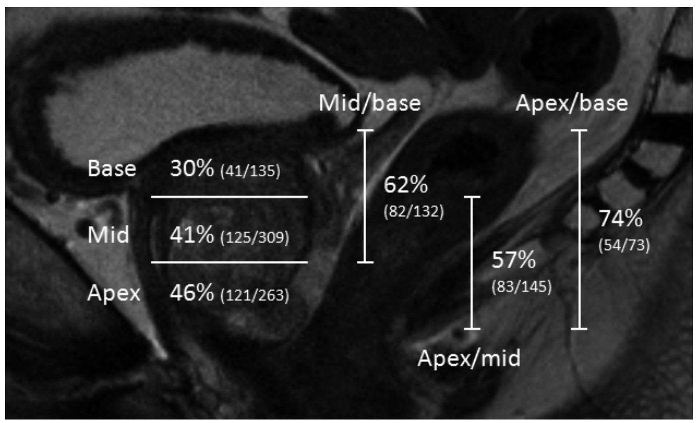
Chi-squared tests were used to calculate for differences in proportions between the zones.
csPCa = clinically significant prostate cancer; PI-RADS = Prostate Imaging Reporting And Data System; TRUS = transrectal ultrasound guided biopsy

Figure 1 Patient flow chart



MRGB = Direct in-bore magnetic resonance imaging guided prostate biopsy; PI-RADS = Prostate Imaging Reporting And Data System; PCa = prostate cancer; GS = Gleason score.

Figure 2 Detection rates differentiated per location



Clinically significant prostate cancer (csPCa) detection rates (%, n) are displayed based on the location of the lesion detected on multiparametric magnetic resonance imaging. E.g. The csPCa detection rate for lesions covering both the mid and apex region of the prostate is 57% (83/145). In table 7, the csPCa detection rates per subcohort are displayed.

Table 7 Location and csPCa detection rates stratified per cohort

(n = 1057)	Biopsy naïve (n = 184) % (n)	Prior negative TRUS (n = 649) % (n)	Active Surveillance (n= 224) % (n)
Apex	39 (16/41)	52 (85/163)	34 (20/59)
Apex/Mid	76 (16/21)	57 (50/88)	47 (17/36)
Mid	47 (32/68)	39 (66/168)	37 (27/73)
Mid/Base	48 (12/25)	66 (57/87)	65 (13/20)
Base	38 (6/16)	28 (27/95)	33 (8/24)
Apex-Base	77 (10/13)	71 (34/48)	83 (10/12)

In figure 2 the entire cohort is displayed. For example, the detection rate of csPCa of lesions covering the entire prostate (Apex-Base) in biopsy naïve patients is 77% (10/13).
csPCa = clinically significant prostate cancer; TRUS = transrectal ultrasound guided biopsy

Biopsy of lesions next to the index lesion

In 298 (28%) patients, one (n = 260) or two (n = 38) other lesions were biopsied next to the index lesion. Overall, in 10% (n = 29) of patients with a second or a third suspicious lesion, the other lesion harbored a more aggressive PCa than the index lesion did. In 3% (n = 9) the index lesion did not result in the detection of PCa at all, whereas the other lesion did harbor GS 3+3 (n = 6), GS 3+4 (n = 2) or GS 4+3 (n = 1). In 4% (n = 11) a GS 3+3 detected in the index lesion was overshadowed by the detection of a GS 3+4 (n = 9) or a GS 4+3 (n = 2) in another lesion and in an additional 3% (n = 9) a GS 3+4 or a GS 4+3 was found in the index lesion while a more aggressive tumor was found in the second or third lesion.

Discussion

Our study demonstrates the largest cohort of MRGB in patients with suspicious lesions scored according to PI-RADS representing daily clinical practice.

As expected, (cs)PCa detection increases with a higher PI-RADS level. The majority of detected PCa is clinically significant. These results are largely similar to results presented by other groups, although, a direct comparison is hard to perform as other groups, for example, included a low number of patients, did not differentiate between the PI-RADS scores or used a 1.5 Tesla MRI instead of a 3.0 Tesla.[7-12] Results between the three cohorts are quite similar, although, in patients in AS the detection of insignificant PCa is higher and the detection of csPCa is lower compared to the other cohorts. In patients in AS, GS 3+3 PCa is already proven to be present, this increases the yield of insignificant PCa within this cohort.

Further, we demonstrated that follow up in patients with negative MRGB findings despite a suspicious finding on prior mpMRI rarely results in csPCa (1.7%). Although patients with a lesion scored PI-RADS 5 are highly likely to have csPCa, in 33% we did not detect csPCa and in 9% we did not detect any PCa. In part, this may be explained by pathology which mimic PCa, for example prostatitis or fibrosis. By contrast, benign prostatic hyperplasia (BPH) also often disturbs the assessment of prostate mpMRI. A highly vascularised BPH nodule, for example, is sometimes incorrectly scored PI-RADS 5.

An important finding of our study is the ability of PSAD to predict biopsy outcome in patients with PI-RADS 3 lesions. Recently, Washino et al.[13] revealed that the PI-RADS score and PSAD were independent factors to predict csPCa and they stated that patients with a PI-RADS ≤ 3 and a PSAD of < 0.15 ng/ml/ml could avoid unnecessary biopsy. Owing to the known high NPV of PI-RADS in lesions classified ≤ 2 with values up to 98-100%, these lesions are not biopsied in our hospital, regardless of the PSAD. [8, 14, 15] Our findings now demonstrate that up to 42% of patients with a PI-RADS 3 classification avoid biopsy when you would decide not to biopsy patients with a PI-RADS 3 and a PSAD below 0.15 ng/ml/ml . In 2-15% of them, csPCa would then be missed. Owing to a higher prevalence of csPCa in patients with a PI-RADS 4 or 5 lesion, PSAD is not useful as a tool to avoid unnecessary biopsy within these cohorts.

More recently, Hansen et al.[15] also evaluated the combination of PI-RADS and PSAD to avoid biopsy in patients with PI-RADS 3 lesions. Based on their and our findings we now suggest avoiding targeted biopsy in patients with a PI-RADS 3 lesion and a PSAD below 0.15 ng/mL/mL. As PSAD incorporates prostate volume, our findings may even support the concept of using prostate volume and PSA blood level together in risk calculators, even before adding prostate imaging in the diagnostic workup. However, the evaluations that we performed specifically address the use of PSAD in patients with a PI-RADS 3, 4 or 5 lesion.

Another interesting finding of our study is that in patients with prior negative TRUS biopsy, a suspicious lesion seen in the PZ is significantly less likely to be csPCa compared to other zones or compared to lesions in the PZ in biopsy naïve patients. Previously, Schouten et al.[16] stated that in patients with prior negative TRUS biopsy, the majority of PCa was detected in the transition zone. Our results confirm these findings, and in addition, we detected that the assessment of the PZ is disturbed in patients with prior negative TRUS biopsy resulting in a lower detection rate. First, this can be explained by the fact that the PZ is already presampled in patients with prior TRUS biopsy, making the yield of additional biopsies in the same area poorer. Second, prostatitis and fibrosis caused by TRUS biopsy mimic and mask PCa in the PZ and thus cause a lower PCa detection

compared with the TZ. Most remarkable in the csPCa detection rates stratified in apex, midgland and base are the higher detection rates in lesions overlapping those regions. This may well be explained by the fact that such lesions are probably larger and thus more likely to be csPCa. Especially in lesions that reach from apex to base, high csPCa detection rates are reached.

Further, our data provide information about the detection of PCa in lesions which are not classified as the index lesion. We detected that in 10% of patients who have had a biopsy in two or more lesions, the index lesion harbored less aggressive PCa compared with the second or third lesion. These findings support the importance of biopsying multiple lesions in case different lesions are detected at mpMRI, as encouraged by PI-RADS version 2.[6]

As far as we know, PI-RADS and MRGB were never evaluated with such a number of patients as we now presented, which allowed us to address several aspects of PI-RADS and subsequent targeted biopsy. This study, however, has some limitations as well. The most important limitation is the retrospective nature of the study. Retrospective studies are known for their risk of selection bias. In addition, a consequence of the retrospective design is the assessment of mpMRI images by different radiologists. Some radiologists involved were highly experienced whereas others were less experienced. Moreover, each radiologist has his/her own way for measuring, for example, prostate size. On the contrary, an advantage of this is that it represents the daily practice we have to deal with. However, we are aware of the fact that our institution is experienced in both prostate mpMRI reading and MRGB. As a consequence, results may be difficult to extrapolate to hospitals with less experience. This study is further limited by the inclusion of patients with differing biopsy histories. To compensate for this limitation, we displayed the biopsy results for each cohort separately as well as all results together. The advantage is that we were able to demonstrate the effect a biopsy history has on PCa detection. Unfortunately, the presented follow up in this study is hampered for two reasons. First, due to the retrospective design, no uniform protocol for follow up was used. Therefore, follow-up consists of targeted, TRUS, TURP and open prostatectomy data. Second, the follow-up data were obtained by reviewing a nationwide network and registry of pathology. As a consequence, we do not know about follow-up of patients without pathology. Prospective studies evaluating long term follow-up after negative biopsies in patients with suspicious lesions are needed to determine the consequences of such a negative biopsy and to comment on the follow-up strategies in such patients. In our study, over 70% did not have follow-up histology. Unfortunately we do not know about any PSA or mpMRI in these patients. The final limitation of this study might be the use of both PI-RADS v1 and PI-RADS v2. Although, the consequence of this is probably limited as studies evaluating the differences between PI-RADS v1 and v2 showed that the diagnostic accuracy between both versions differs minimally.[17-20] A limitation, not related to this study, is the inability of performing systematic biopsy next to targeted biopsy in MRGB. Studies evaluating the added value of systematic TRUS biopsy next to targeted biopsy are reporting up to 10% of csPCa detected with TRUS biopsy which would be missed in a targeted-only approach. Therefore, there is still room for debate whether or not to add 10-12 core systematic TRUS biopsy next to targeted biopsy.[12, 21, 22]

Conclusions

MRGB in previous negative biopsy cases yields high csPCa detection rates in PI-RADS ≥ 3 and the use of PSAD in patients with PI-RADS 3 enables them to avoid unnecessary biopsy. Despite the high performance of mpMRI and MRGB, in some patients with suspicious mpMRI findings pathology does not reveal PCa. However, follow-up histology in such patients rarely results in csPCa. Additional research with prospectively collected data is needed to verify our findings.

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4

Retrospective comparison of direct in-bore magnetic resonance imaging (MRI)-guided biopsy and fusion-guided biopsy in patients with MRI lesions which are likely or highly likely to be clinically significant prostate cancer

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Abstract

Purpose To compare clinically significant prostate cancer (csPCa) detection rates between Magnetic Resonance Imaging (MRI) – transrectal ultrasound (TRUS) fusion-guided prostate biopsy (FGB) and direct in-bore MRI-guided biopsy (MRGB).

Methods We performed a comparison of csPCa detection rates between FGB and MRGB. Included patients had (1) at least one prior negative TRUS biopsy; (2) a Prostate Imaging Reporting and Data System (PI-RADS) 4 or 5 lesion and (3) a lesion size of ≥ 8mm measured in at least one direction. We considered a Gleason score ≥ 7 being csPCa. Descriptive statistics with 95% confidence intervals (CI) were used to determine any differences.

Results We included 51 patients with FGB (59% PI-RADS 4 and 41% PI-RADS 5) and 227 patients with MRGB (34% PI-RADS 4 and 66% PI-RADS 5). Included patients had a median age of 69 years (IQR, 65-72) and a median PSA level of 11.0 ng/ml (IQR, 7.4-15.1) and a median age of 67 years (IQR, 61-70), the median PSA 12.8 ng/ml (IQR, 9.1-19.0) within the FGB and the MRGB group respectively. Detection rates of csPCA did not differ significantly between FGB and MRGB, 49% vs. 61% respectively

Conclusion We did not detect significant differences between FGB and MRGB in the detection of csPCa. The differences in detection ratios between both biopsy techniques are narrow with an increasing lesion size. This study warrants further studies to optimize selection of best biopsy modality.

Introduction

Several major changes have taken place in the last decade regarding the diagnosis of prostate cancer (PCa). Most important is the introduction of multiparametric magnetic resonance imaging (mpMRI). mpMRI allowed for an accurate detection and localization of clinically significant (cs)PCa. It also made it possible to perform targeted biopsy instead of 10-12 core systematic transrectal ultrasound (TRUS) guided biopsy and it thus enables to reduce the number of biopsy needles.[1,2] Nowadays, mpMRI is recommended by the European Association of Urology (EAU) in men with a persistent clinical suspicion of PCa despite a negative TRUS biopsy.[3] These recommendations are made because TRUS biopsy is under-diagnosing csPCa, especially in lesions anteriorly located in the prostate.[4]

After mpMRI, suspicious areas can be targeted using the obtained information. Targeted biopsy can be done, for example, direct in-bore MR-guided (MRGB). MRGB is able to accurately target suspicious lesions; however, the procedure is time-consuming, expensive and in most countries very limited accessible.[5,6] For these reasons, MRI-TRUS fusion guided biopsy (FGB) is more commonly performed. In FGB, previously obtained mpMRI information is fused (cognitively or software assisted) with real-time TRUS images. MR “slot-time” can be saved because the biopsy can be performed ultrasound-guided rather than MR-guided. This enable the procedure to be less expensive and much more readily available. Also, FGB allows a urologist to perform a 10-12 core systematic TRUS biopsy in addition to targeted biopsy as systematic TRUS biopsy still detects csPCa in up to 10% of patients which would be missed in a targeted only-approach.[7-9] In our institution, only patients with lesions larger than 8mm measured in at least one direction are considered eligible for FGB as we expected FGB in those lesions to be as accurate as MRGB.[10,11]

With FGB and MRGB increasingly being practiced, there is a need to determine whether those techniques yields comparable csPCa detection rates. Nowadays, as far as we know, only one study was performed which compared the two targeted biopsy approaches.[12] Therefore, the aim of our study is to compare the difference in the detection of csPCa between both biopsy procedures.

Methods

Patients

In our institution, 82 patients had FGB between December 2014 and December 2016. Of these patients, 51 met the next inclusion criteria: (1) at least one prior negative TRUS biopsy; (2) a Prostate Imaging Reporting and Data System (PI-RADS) 4 or 5 lesion localized on prior mpMRI performed in our institution and (3) a lesion size of ≥ 8mm measured in at least one direction. To compare, we searched our institutional MRGB database, starting from January 2012. This reference database contained 227 patients with the same inclusion criteria. The study was approved by our institutional review board.

mpMRI

mpMRI was performed on a 3.0 T MR-scanner (Siemens, Skyra) with a pelvic phased-array coil. Tri-planar anatomical T2- weighted images (T2W), axial dynamic contrast-enhanced images (DCE) and axial diffusion-weighted (DW) images were obtained. Images were analyzed and reported according to PI-RADS version 1 or 2 by six radiologist with varying experience in prostate MR reading (2-20 yr).[13,14]

Software assisted registration

Prior to the FGB procedure, Digital Imaging and Communications in Medicine (DICOM) images were uploaded to the ultrasound device (Aplio 500, Toshiba Medical Systems). An electromagnetically (EM) tracking field generator was placed near the pelvis of the patient and an EM tracking sensor was attached to the free-hand operated transrectal ultrasound probe (PVT-781 VT) so that real-time movement tracking is allowed. Uploaded axial T2W images and ultrasound images were displayed side by side. Rigid image registration was acquired by selecting landmarks visible on both the ultrasound images and the uploaded T2W images. A landmark (e.g. cysts, verumontanum or BPH nodules) as close as possible to the suspicious lesion was chosen to enable the most reliable registration. After software assisted registration, we cognitively enhanced the fusion as rigid image registration is often distorted by the deformation of the prostate caused by the introduction of the ultrasound probe for example. We only performed targeted biopsy without additional 10-12 core random biopsy. Procedure time was typically 10-20 minutes. The procedure was performed without using anesthetics. The described registration method does not allow for a confirmation of the needle position in the prostate.

As our institution was much more experienced in MRGB at the time of the introduction of FGB in our hospital, we offered FGB only to patients with a PI-RADS 4 or 5 lesion and a lesion size of ≥ 8mm measured in at least one direction. Patients with smaller lesions and lesions scored PI-RADS 3 were immediately offered MRGB. Patients who preferred MRGB over FGB were offered MRGB and vice versa. FGB was performed by one radiologist without prior prostate biopsy experience.

Direct in-bore MR-guided biopsy

During MRGB, patients are positioned in a prone position. A needle guide is rectally inserted. Prior to biopsy, additional axial T2W and axial DW images were made to confirm the localization of the lesion. True fast imaging with steady-state free precession (TRUFI) images were used to direct the manually adjustable needle guide. After each biopsy, the position of the needle was confirmed with TRUFI images. The accuracy of the needle position was assessed by one of the prostate MR experienced radiologists. No anesthetics were used during this procedure. All biopsies were performed transrectal without adding 10-12 core systematic TRUS biopsies. Procedure time is typically 45-60 minutes.

Histopathology

All biopsy cores were evaluated by one of three dedicated uropathologist. Pathologists were not blinded for the biopsy method or the mpMRI findings. We considered a Gleason score ≥ 7 being clinically significant. In case a patient does have multiple lesions, we used the index lesion (according to PI-RADS) for the analysis. In case a patient had a lesion next to the index lesion which did not match the inclusion criteria, we did biopsy the lesion, however, we did not evaluate the results in this study.

Statistical analysis

We used descriptive statistics with 95% confidence intervals (CI) with a continuity correction factor to calculate potential differences between the two techniques. Additionally, we used chi-square statistics to calculate for significant differences between cohorts. A p-value ≤ 0.05 was considered statistically significant. Analyses were conducted using IBM SPSS Statistics (Version 22).

Results

Patient characteristics

The 51 included patients having FGB had 58 lesions to target. Those patients had a median age of 69 years (IQR, 65-72) and a median PSA level of 11.0 ng/ml (IQR, 7.4-15.1). They had a median of 2 (IQR, 1-2) previous negative TRUS biopsy sessions and had a median PSA density 0.18 ng/ml/ml (IQR, 0.1-0.3). Overall, 58.8% (30/51) were biopsied because of a PI-RADS 4 index lesion and 41.2% (21/50) because of PI-RADS 5.

The 227 patients in the reference database having MRGB had 261 biopsied lesions. The median age was 67 years (IQR, 61-70), the median PSA 12.8 ng/ml (IQR, 9.1-19.0) and the median PSA density ng/ml/ml 0.23 (IQR, 0.15-0.40). Patients had a median of 2 (IQR, 1-3) prior negative TRUS biopsy sessions. Overall, 33.9% (77/227) were biopsied because of a PI-RADS 4 index lesion and 66.1% (150/227) because of PI-RADS 5. Further patient and lesion characteristics are specified in table 1.

Table 1 Patient and lesion characteristics

Patient characteristics	FGB (n = 51)	MRGB (n = 227)
Age, yr, median (IQR)	69 (65-72)	67 (61-70)
PSA level, ng/ml, median (IQR)	11.0 (7.4-15.1)	12.8 (9.1-19)
Prostate volume, ml, median (IQR)	63.0 (46-86.0)	53.0 (36.5-78.0)
PSA density, ng/ml/ml, medain (IQR)	0.18 (0.1-0.3)	0.23 (0.15-0.4)
PI-RADS score index lesion, n (%)		
4	30 (58.8)	77 (33.9)
5	21 (41.2)	150 (66.1)
Time between mpMRI and biopsy, days, median (IQR)	28 (21-43)	29 (17-42)
No. of prior TRUS biopsies, median (IQR)	2 (1-2)	2 (1-3)
Lesion characteristics	**FGB (n =58)**	**MRGB (n = 261)**
PI-RADS score, n (%)		
4	37 (63.8)	101 (38.7)
5	21 (36.2)	160 (61.3)
Biopsies per lesion, n, median (IQR)	3 (2-3)	2 (2-3)

FGB = fusion guided biopsy; MRGB = direct in-bore magnetic resonance guided biopsy; yr = year; IQR = Inter quartile range; PSA = prostate specific antigen; PI-RADS = Prostate Imaging Reporting and Data System; mpMRI = multiparametric magnetic resonance imaging; TRUS = transrectal ultrasound guided biopsy

Prostate cancer detection

In patients having FGB, csPCa was detected in 49.0% (25/51) and any PCa in 66.7% (34/51). The csPCa detection rate in patients with PI-RADS 4 or 5 was 33.3% (10/30) and 71.4% (15/21) respectively. In these subcohorts, any PCa was detected in 56.7% (17/30) and 81.0% (17/21) respectively.

The detection rates in patients having MRGB were 61.2% (139/227) for csPCa and 85.0% (193/227) for any PCa. This is a difference in favor of MRGB of 12.2 ($p = 0.11$) and 18.3 ($p < 0.05$) percentage points respectively.

The csPCa detection rates favored MRGB in patients with a lesion scored PI-RADS 4 with 16.0 ($p = 0.13$) percentage points. In patients with PI-RADS 5, FGB reached a csPCa detection rate which was 4.1 ($p = 0.71$) percentage points higher than that of MRGB (table 2).

Figure 1 and 2 represent the csPCa and any PCa detection rates respectively per (sub)cohort of both techniques with 95% confidence intervals.

Table 2 Detection rates of (cs)PCa

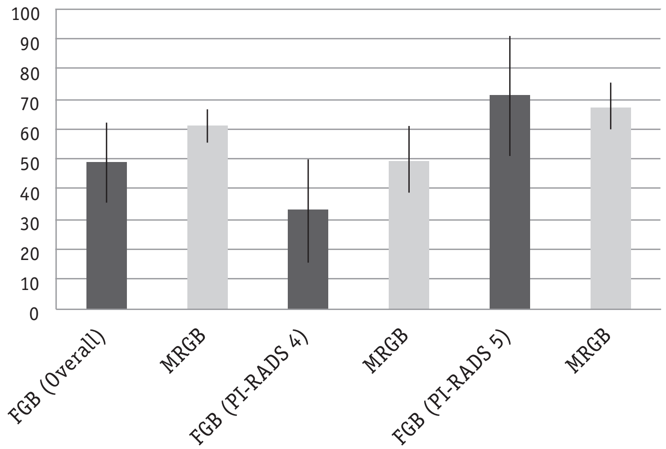
Detection rates	FGB (n = 51)	MRGB (n = 227)	Difference, (95% CI)
Overall			
any PCa, % (n)	66.7 (34)	85.0 (193)	18.4 (5.0 – 33.7)
csPCa, % (n)	49.0 (25)	61.2 (139)	12.2 (-3.5 – 27.6)
PI-RADS 4	n = 30	n = 77	
any PCa, % (n)	56.7 (17)	72.7 (56)	16.1 (-4.8 – 37.2)
csPCa, % (n)	33.3 (10)	49.4 (38)	16.0 (-6.6 – 35.3)
PI-RADS 5	n = 21	n = 150	
any PCa, % (n)	81.0 (17)	91.3 (137)	10.4 (-3.7 – 34.2)
csPCa, % (n)	71.4 (15)	67.3 (101)	4.1 (-20.7 – 22.4)

FGB = fusion guided biopsy; MRGB = direct in-bore magnetic resonance guided biopsy; PCa = prostate cancer; cs = clinically significant (Gleason score ≥ 7); PI-RADS = Prostate Imaging Reporting and Data System. Differences are shown in percentage points

csPCa detection correlated to lesion size

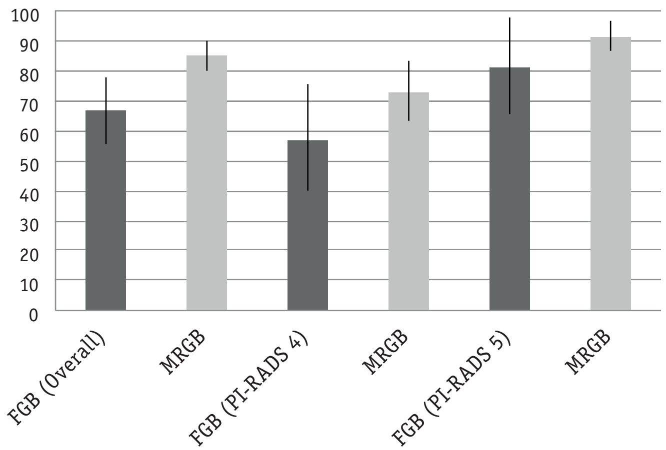
Applying a minimal lesion size of 16mm instead of 8mm increases the csPCa detection rate from 49% (95% CI, 35.0-63.2) to 61.5% (95% CI, 40.7-79.1) for FGB and from 61.2% (95% CI, 54.5-67.5) to 63.9% (95% CI, 55.1-71.9) for MRGB. Further increasing the minimal lesion size to 24mm results in a csPCa detection ratio of 63.6% (95% CI, 31.6-87.6) and 67.3% (95% CI, 53.2-79.0) for FGB and MRGB respectively. In figure 3 the detection ratios for csPCa are displayed correlated with the minimal lesion size.

Figure 1 CsPCa detection of FGB and MRGB



CsPCa detection rates of FGB and MRGB displayed overall and per PI-RADS classification. The bar chart represents the detection rates and the black lines indicate the 95% confidence intervals.
csPCa = clinically significant prostate cancer (Gleason score ≥ 7); FGB = fusion guided biopsy; direct in-bore magnetic resonance imaging guided biopsy; PI-RADS = Prostate Imaging Reporting and Data System

Figure 2 Any PCa detection of FGB and MRGB



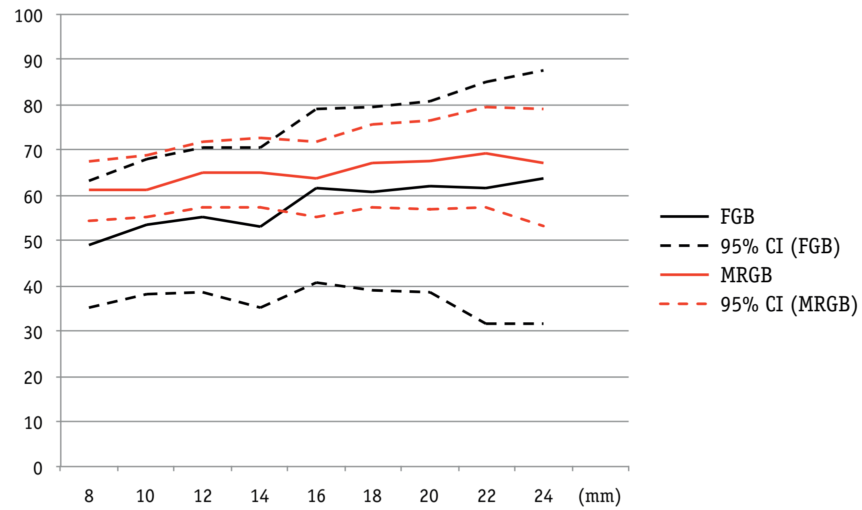
PCa detection rates of FGB and MRGB displayed overall and per PI-RADS classification. The bar charts represent the detection rates and the black lines indicate the 95% confidence intervals.
PCa = prostate cancer; FGB = fusion guided biopsy; MRGB = direct in-bore magnetic resonance imaging guided biopsy; PI-RADS = Prostate Imaging Reporting and Data System

The detection rate of any PCa for FGB increases from 66.7% (95% CI, 52.0-78.9) with a minimal lesion size of 8mm to 73.1% (95% CI, 52.0-87.7) and 81.8% (95% CI, 47.8-96.8) in case lesions of 16mm or 24mm would have been biopsied respectively. Detection rates of any PCa for MRGB would increase from 85.0% (95% CI, 79.6-89.3) to 88.7%(95% CI, 81.8-93.3) and 90.9% (95% CI, 79.3-96.6) applying a minimal biopsy threshold of 16 and 24mm respectively. In figure 4 we supplied the detection rates of any PCa with 95% CI with different minimal lesion sizes.

Follow up after negative fusion guided biopsy

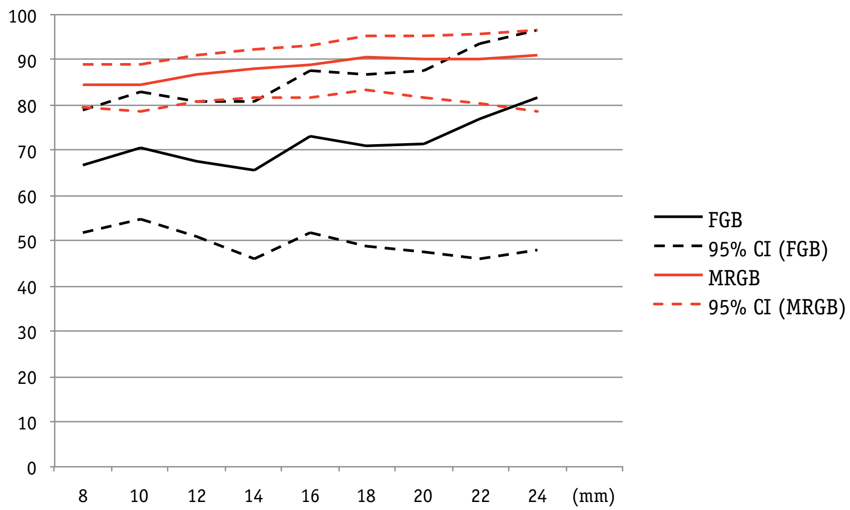
Within the cohort of 17 patients with a negative biopsy outcome after FGB, two patients a follow up (FU) MRGB performed within two months. In both PCa was detected: in one a GS 3+3 and in one a GS 2+3. In one patient, a radiologist downgraded the level of suspicion from PI-RADS 5 to PI-RADS 2 after another mpMRI was performed a year after FGB. In another five patients, PSA decreased and therefore no follow up mpMRI was performed. In the remaining nine patients, follow up is unknown.

Figure 3 csPCa detection with different lesion sizes



csPCa detection rates and 95% CI for both FGB and MRGB with different lesion sizes in millimeters. The dotted lines represent the 95% CI. csPCa = clinically significant prostate cancer; CI = confidence interval; FGB = fusion guided biposy; MRGB = direct in-bore magnetic resonance imaging guided biopsy; mm= millimeter

Figure 4 Any PCa detection with different lesion sizes



Any PCa detection rates and 95% CI for both FGB and MRGB with different lesion sizes in millimeters. The dotted lines represent the 95% CI. PCa = prostate cancer; CI = confidence interval; FGB = fusion guided biposy; MRGB = direct in-bore magnetic resonance imaging guided biopsy; mm= millimeter

Discussion

This study evaluated the performance of FGB compared to MRGB. We did not detect statistically significant differences between FGB and MRGB for csPCa in patients with lesions scored PI-RADS 4 or 5 with a minimal lesion size of 8mm measured in at least one direction (49% vs 61%). We neither detected statistically significant differences when evaluating the results for PI-RADS 4 and 5 separately.

As far as we know, at the moment, only Arsov et al.[12] performed a study in which two MR-targeted prostate biopsy approaches were compared. They compared PCa detection rates between an MRGB approach alone and a FGB approach combined with systematic TRUS biopsy. As interim analyses did not identify an important improvement in detection rates for the combined approach, the study was halted. Evaluating their results, exclusively comparing the two targeted biopsy approaches, in-bore biopsy reaches a csPCa detection rate of 29% (31/106) compared to a detection rate of 26% (27/104) in patients having FGB.

As Arsov et al, we did not detect significant differences in csPCa detection rates. Remarkably, the csPCa detection rates in our study are higher than those of Arsov et al., this could be well explained by the differences in used inclusion criteria. We only included patients with lesions scored PI-RADS 4 or 5 and a minimal lesion size of 8mm. Therefore our results cannot be reliably compared with their results.

Comparing the cohorts in our study for PI-RADS 4 and 5 separately, we demonstrated a slightly lower csPCa detection rate in PI-RADS 4 lesions for FGB, although, this result was not statistically significant. On the other hand, in patients with a PI-RADS 5 lesion, the detection rate of csPCa is slightly higher in the cohort having FGB, again, this was not a statistically significant difference. The higher detection rate for FGB in lesions score PI-RADS 5 is probably caused by the fact that a PI-RADS 5 lesion is most commonly larger than a lesion scored PI-RADS 4. With both FGB and MRGB experience, we noticed that larger lesions and lesions with a PI-RADS score of 5 are often visible on ultrasound during FGB, which allowed us to target such lesions accurately. This is supported by the results of our evaluation of detection rates correlated to the lesion size as displayed in figure 3 and 4. The difference in detection rates between the two biopsy techniques narrows when applying a higher threshold for the minimal lesion size. These results however should be evaluated with caution. The sample size is getting smaller when increasing the threshold of the lesion size and, as a consequence, the 95% CI is widening. However, in our institution, both FGB and MRGB are being practiced. As we used a fusion platform based on rigid image registration, a cognitive enhancement is required to biopsy a suspicious lesion reliably. This enhancement is most reliable in case a lesion appears to be visible on gray scale ultrasound after the software assisted rigid image registration is completed. We observed that most cases required a cognitive enhancement. Though, in most cases cognitive enhancement was possible as lesions often appears to be visible on grayscale ultrasound after the software assisted image registration was performed. Especially the lesions scored PI-RADS 5 and the lesions with a larger diameter. This suggestion is supported by the presented data as the detection rate of csPCa in lesions scored PI-RADS 5 are almost equal between both biopsy techniques. Further, the differences in detection rates of both biopsy techniques narrows when applying a higher threshold of lesions sizes from where to biopsy. A further increase in ultrasound visibility of lesions may be reached by adding other ultrasound modalities like power Doppler or elastography, this may increase the diagnostic accuracy of FGB based on a rigid image registration system.[15,16]

At the moment, the studies investigating csPCa detection rates between different MR targeted biopsy approaches did not detect statistically significant differences. In our study this may be explained by the use of a retrospective study design with a relatively small sample size, which is an important limitation of our study. A prospective trial should be performed to investigate potential relevant differences between both biopsy techniques. Unfortunately, the prospective trial of Arsov et al.[12], which tried to address this issue, was halted and thus did not reach their required sample size. Of course, the question arises which differences in detection rates are allowed as FGB is less expensive compared to MRGB and it thus may be less accurate. To assess the required diagnostic accuracy of FGB, Health Technology Assessment studies could be helpful.

A limitation of our study is that we performed a single centre study. As a consequence, we performed FGB and MRGB on one type of machine, while nowadays, several commercially available platforms are used worldwide. In the future, a multicentre study could solve this limitation.

In our institution, only patients with lesions larger than 8mm measured in at least one direction are considered eligible for FGB as we beforehand expected FGB to be slightly less accurate than MRGB. Thus, the results of this study does not cover lesions which are quite small. This raises the question whether FGB is an appropriate technique to target such small lesions. Unfortunately, our data is not appropriate to address this question.

Another limitation of our study is the different number of included patients in both cohorts making comparisons difficult. It would have been desirable to increase the FGB cohort, for instance to eliminate the learning curve we had. To maximize the MRGB cohort, we used a longer inclusion for that cohort. It is clear that our institution is much more experienced in MRGB than in FGB which may introduce a bias in favor of MRGB. Unfortunately, FGB was introduced in our institution at a later time.

A last limitation of our study is the distribution of PI-RADS 4 and 5 in both subgroups. The FGB cohort consists of approximately 40% of patients with a PI-RADS 5 lesion while this almost 70% in the MRGB cohort. This is likely to influence the results in favor of MRGB.

Our findings support our persuasion of FGB having an important role in the diagnosis of csPCa in patients with suspicious lesions seen on mpMRI, especially in larger lesions. Compared to MRGB, FGB is a relatively simple technique to implement in urologist's practice. Procedure time for example is considerably shorter for FGB. Further, in most countries MR "slot-time" is expensive and very limited available making FGB a less expensive and thus a more attractive procedure. Further, FGB allows you to perform 10-12 core systematic TRUS biopsy next to targeted biopsy which may be important as several studies are reporting up to 10% of detected csPCa with systematic biopsy which would be missed in a targeted-only approach.[7,8] MRGB appears to be a method reserved for the institutions that are in the position to use MR "slot-time" for this procedure.

Conclusion

We did not detect significant differences between FGB and MRGB in the detection of csPCa. The differences in detection ratios between both biopsy techniques narrows with an increasing lesion size. This study warrants further studies to optimize selection of best biopsy modality.

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5

Yield of repeat targeted direct in-bore magnetic resonance-guided prostate biopsy (MRGB) of the same lesions in men having a prior negative targeted MRGB

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Abstract

Background This study's endpoints were to determine the yield of repeat MRGB (MRGB-2) after the first one was found to be negative (MRGB-1), in order to correlate with clinical parameters and to present the subgroup analyses of patients with positive repeat biopsies, despite having a negative initial biopsies.

Materials and Methods We retrospectively included patients with MRGB-2 after a negative MRGB-1 both between January 2006 and August 2016. All anonymized MRI data were retrospectively reassessed according to the PI-RADS version 2 by two radiologists. Images of MRGB were compared to determine whether the same prostate lesion was biopsied during MRGB-1 and MRGB-2. Descriptive statistics were utilized to determine the yield of clinically significant prostate cancer (csPCa) at MRGB-2. Gleason score of ≥3+4 was considered csPCa. This study included 62 patients (median age, 63 years; interquartile range [IQR], 58-66 years) with 75 sampled lesions during MRGB-2 left for analysis, and 63 lesions were resampled and 12 new lesions were sampled. Included are patients who had a prostate-specific antigen (PSA) at MRGB-1 of 13 ng/ml (IQR,5.8-20) and a PSA at MRGB-2 of 15 ng/ml (9.0-23).

Results In 16/75 (21%) lesions csPCa was detected during MRGB-2. Of 63 resampled lesions, 13 (21%) harbored csPCa at MRGB-2. In two patients, csPCa was detected on repeat biopsy, while the volume of the lesion decreased between MRGB-1 and MRGB-2.

Conclusion We concluded that patients could benefit from repeat biopsy after negative initial MRGB, especially in the case of increasing PSA values and persisting PCa suspicion in MRI. Further research is needed to establish predictors for positive repeat targeted biopsies.

Introduction

Since its introduction, multiparametric magnetic resonance imaging (mpMRI) of the prostate and subsequent targeted biopsy improved the detection of clinically significant prostate cancer (csPCa), without increasing the detection of insignificant prostate cancer when (PCa) compared to a systematic transrectal ultrasound (TRUS)-guided biopsy.[1-3] Reported csPCa detection rates of the targeted biopsy (e.g., fusion-guided or direct in-bore MR targeted) in men with a suspicious lesion ranged from 17-52%, with several reasons for this serious range. Some of these reasons are the diverse definitions for csPCa, the various thresholds from where a lesion is biopsied, the ranging MRI protocols and the differences in study protocols being either prospective or retrospective.[1, 4-9] Detection rates for any PCa even ranges from 22-79% in men with lesions detected on prebiopsy mpMRI.[4, 6, 10, 11] Contrariwise, when a biopsy did not reveal any PCa in 21-78% of those men, although they had a suspicious lesion seen on mpMRI. In our institution, such patients, in whom direct in-bore MR-targeted biopsy (MRGB) was negative despite a suspicious lesion, are frequently followed by measuring the serum prostate-specific antigen (PSA) and if required, obtaining another mpMRI or even repeating theMRGB. Consequently, additional costs are being made and patients are subjected to risks and the inconvenience associated with it.

Previously, Chelluri et al.[12] described their findings in 90 men having a second MRI-TRUS fusion guided biopsy after the first one was negative, yielding a 6.0% Gleason score ≥ 3+4 lesions. In addition, recently Costa et al.[13] presented their results yielding 40% of intermediate and high risk cancers with repeat targeted biopsies or surgeries in 38 highly suspicious lesions with an initial negative MRI-TRUS fusion targeted prostate biopsy.

To our knowledge, the yield of repeated MRGB in this particular clinical scenario is not well established. This is especially interesting as direct in-bore MR targeted biopsy is still the most accurate prostate biopsy technique. [7, 14, 15] Therefore, the aim of our paper was to determine the yield of repeat direct in-bore MRGB (MRGB-2) in patients having a negative first one (MRGB-1) and to correlate with clinical parameters and to present subgroup analyses of patients with positive repeat biopsies despite having negative initial biopsies.

Materials and Methods

This retrospective study was approved by our institutional review board with a waiver of informed consent (2016-2767).

Patients

The Picture Archiving and Communication System (PACS) data was searched for patients who had at least two consecutive MRGBs in our institution between January 2006 and August 2016. Patients were excluded if any PCa was detected before MRGB-1 or between MRGB-1 and MRGB-2. Thus, included patients did not have a biopsy proven PCa before MRGB-1, had a negative MRGB-1, had a lesion which was rebiopsied during MRGB-2 and had an mpMRI before MRGB-1 (figure 1). As a consequence of these criteria, we could not provide the results of the overall detection rates during MRGB-1 or MRGB-2.

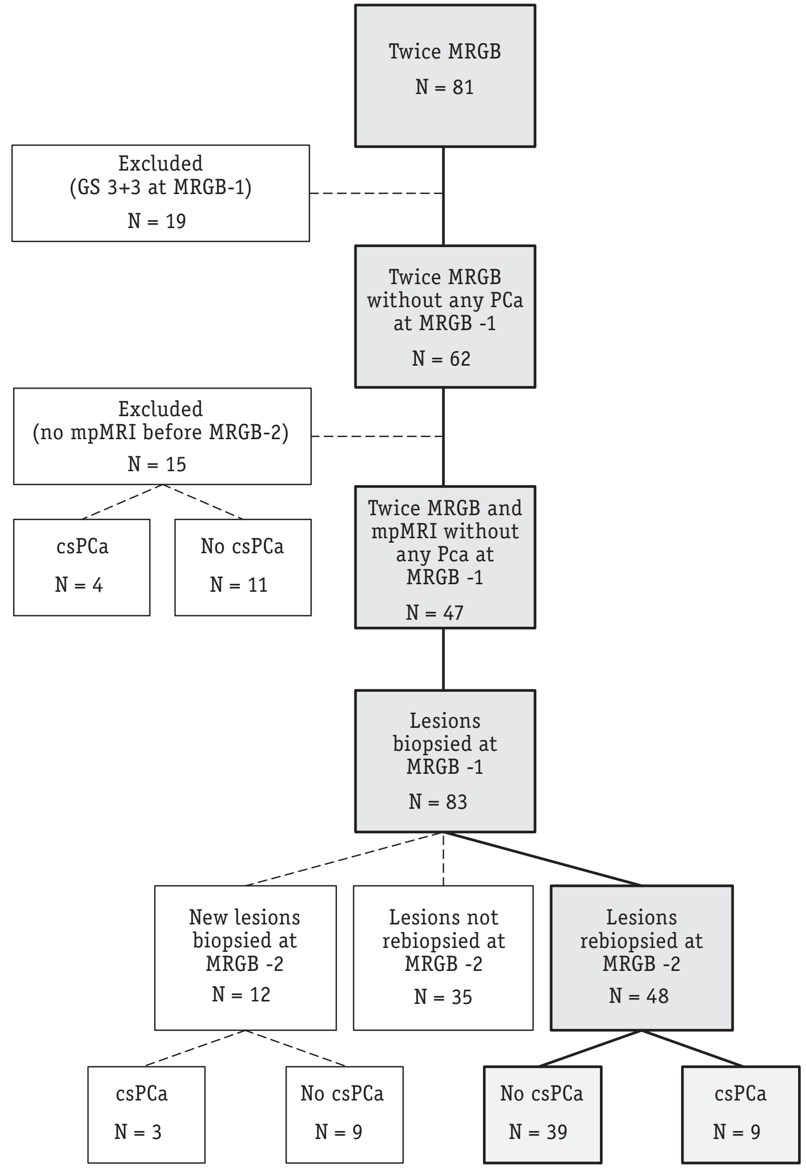
In 81 patients, an MRGB was performed twice in the same patient between January 2006 and August 2016. Of those patients, 19 were excluded because they had a GS 3+3 after MRGB-1.

After exclusion, 62 patients were included with 98 lesions biopsied during MRGB-1. Seven patients were biopsy negative prior to MRGB-1. During MRGB-2, 63 of those lesions were rebiopsied and 12 new lesions were found. In 3 out of these 12 new biopsied lesions, csPCa was detected. Overall, 35 lesions biopsied during MRGB-1 were not rebiopsied during MRGB-2 (Figure 1), because they were not visible anymore or not suspicious for csPCa at mpMRI-2 (i.e., PI-RADS classification 1 or 2). However, because of a lack of pathologic confirmation in those lesions, we did not evaluate this any further. Patient characteristics can be found in Table 1.

MpMRI and MRGB specifications

MRI was performed on a 3T MR-scanner (Siemens, Skyra), with a pelvic phased-array coil. In four patients an endorectal coil was utilized during first mpMRI instead of a pelvic phased-array coil. In all patients, tri-planar anatomical T2-weighted images (T2WI), axial dynamic contrast-enhanced images (DCE) and axial diffusion-weighted images (DWI) were usually obtained. However, because of the large time span in which patients were included, there is a slight variation in mpMRI technical specifications. A typical T2WI sequence had a repetition time (TR) of 3540 ms (range, 3000-7170), an echo time (TE) of 104 ms (range, 99-121), a flip angle of 120 degrees (range, 120-170), a turbo factor of 15 (range, 15-25), a matrix of 320 × 320 pixels (range, 224 × 448 - 384 × 384), and a slice thickness of 3 mm (range, 3-4), with 15 to 27 slices were needed to cover the entire prostate. DWI typically consisted of a calculated ADC map and multiple b-values (0, 50, 500, 800, 1400), a matrix of 128 ×108 pixels (range, 100 × 100 – 144 x 192) with a slice

Figure 1 Flowchart and in- and exclusion criteria of patients with repeat MRGB in our institution



MRGB = magnetic resonance imaging guided biopsy; GS = Gleason score; PCa = prostate cancer; mpMRI = multiparametric magnetic resonance imaging; cs = clinically significant

Table 1 Patient and lesion characteristics of included patients

	csPCa on rebiopsy		Total
	Yes (n = 13)	**No (n = 50)**	
Age (yrs) at MRGB1, median (IQR)	65 (58.5-67.5)	62.5 (58-66)	63 (58-66)
Prior no. TRUS biopsy, median (IQR)	2 (0.5-2.5)	2 (1-3)	2 (1-3)
Prostate volume (ml), median (IQR)	53 (47-61)	47 (41-54)	49 (43-60)
PSA density (ng/ml/ml) before MRGB-1, median (IQR)	0.18 (0.09-0.34)	0.17 (0.11-0.35)	0.17 (0.11-0.35)
PSA (ng/ml) before MRGB-1, median (IQR)	9.9 (4.8-21.2)	14.0 (6.0-19.7)	12.6 (5.8-20.0)
PSA (ng/ml) before MRGB-2, median (IQR)	12.2 (8.5-21.7)	15.6 (9.2-22.9)	15.0 (9.0-22.5)
PSA (ng/ml) increase, median (IQR)	2.7 (0.8-9.3)	1.5 (0.2-7.4)	1.8 (0.05-7.35)
MRGB-1-MRGB-2 (months), median (IQR)	11.0 (2-28.5)	13.0 (5.8-25.0)	13 (5-24.0)
Biopsies per lesion during MRGB-1, n, median (IQR)	2 (2-3)	2 (2-3)	2 (2-3)
Biopsies per lesion during MRGB-2, n, median (IQR)	2 (2-3)	2 (2-3)	2 (2-3)
PI-RADS score, % (n)			
2	19 (6)	81 (26)	(32)
3	20 (1)	80 (4)	(5)
4	11 (2)	89 (17)	(19)
5	57 (4)	43 (3)	(7)
Insignificant PCa detection during MRGB-2, n	-	20	20

Analysis was done on a per lesion basis. In seven patients two lesions were rebiopsied, so their age, prior no. of TRUS biopsy and PSA is twice included in this analysis. MRGB = magnetic resonance imaging guided biopsy; IQR = interquartile range; csPCa = clinically significant prostate cancer; TRUS = transrectal ultrasound guided biopsy; PSA = prostate specific antigen; mpMRI = multiparametric magnetic resonance imaging.

thickness of 4 mm (range, 3-5) with 20 (range, 15-23) slices to cover the prostate. DCE was obtained using 15 ml gadoterate meglumine (Dotarem; Guerbet LCC, Bloomington, IN, USA) with an injection rate of 2.5 ml/s followed by a 20 ml NaCl flush, an acquisition time of 2.5 min (range, 2-6) and a TR of 32 ms (range, 32-44). Patient characteristics are listed in table 1, and follow up after MRGB-2 until September 15, 2017 were acquired from hospital records by one observer (WV).

During MRGB, patients were placed in the prone position with an MR-compatible needle guide rectally inserted. The needle guide was attached to a biopsy device DynaTRIM (Invivo corp., Gainesvill, FL, USA). During the MRGB session, axial T2WI and axial DWI were obtained to reproduce a lesion's location. The needle guide was manually positioned using true fast imaging with steady-state free precession (TRUFI) images. An MR-compatible 18-gauge biopsy gun was used to obtain biopsy cores. The lengths of the obtained cores were 17 mm. Usually, two cores per lesion are obtained. Immediately after the biopsy, with the biopsy needle still inserted, TRUFI images in two directions were obtained to confirm biopsy position. The position of the needle was assessed by one of the radiologists experienced in prostate MR readings. In case there is uncertainty about the accuracy of a needle, a third biopsy core was obtained. The ideal location of the needle is when the tip is piercing through the lesion as the tip of the needle does not obtain tissue. During MRGB, no anesthetics were utilized. Obtained pathological tissue was interpreted by dedicated pathologists with 20-30 years of experience in prostate specimen analysis. Procedure time for MRGB was typically 45-60 min.

MpMRI analysis

Nowadays, in our institution, the threshold for biopsying a lesion is PI-RADS ≥ 3. However, as patients had mpMRI and MRGB before 2012, not every lesion included was scored according to PI-RADS. Therefore, for this study, mpMRI images were anonymized and they were reassessed according to the Prostate Imaging - Reporting and Data System (PI-RADS) version 2 by two radiologists with 5 and 17 years of experience in prostate MR readings (SJ and TT respectively).(16) Disagreements were resolved by consulting a third reader with 12 years of experience in prostate MR readings (JF). MRGB images were used to assess whether the same lesion was rebiopsied during MRGB-2. Only the lesions which were biopsied twice were reassessed. In case other lesions were detected, we did not evaluate them in this study. Radiologists were blinded for pathological outcomes of MRGB-2 but were aware of the negative outcomes of MRGB-1. Lesion volume was calculated by the ellipsoid formula ([left-right × anterior-posterior × cranial-caudal diameter] × ϖ/6). The averages of the calculated volumes were used in the analyses.

Analysis

Descriptive statistics were used for the patient, lesion characteristics and the detection rates of MRGB-2. Inter-observer agreement for final PI-RADS classification between both radiologists was calculated using weighted kappa values. Gleason score (GS) ≥3+4 was assumed to be csPCa.

Results

Yield of repeat MRGB

During MRGB-2, 16 of 75 (21%) biopsied lesions resulted in csPCa. Of 63 rebiopsied lesions, 33 (52%) showed PCa and 13 (21%) csPCa. Six lesions harbored GS 3+4, two GS 4+3, two GS 3+5, one GS 5+3 and two GS 4+5. The median volume of lesions with detected csPCa at repeat biopsy was 0.67ml (0.39-2.1) and the median increase in volume of these lesions was 0.43 ml (interquartile range [IQR], -0.080 – 0.70). Lesion location was represented in Table 2.

Table 2 Location of a lesion correlated to the detection of (clinically significant) prostate cancer

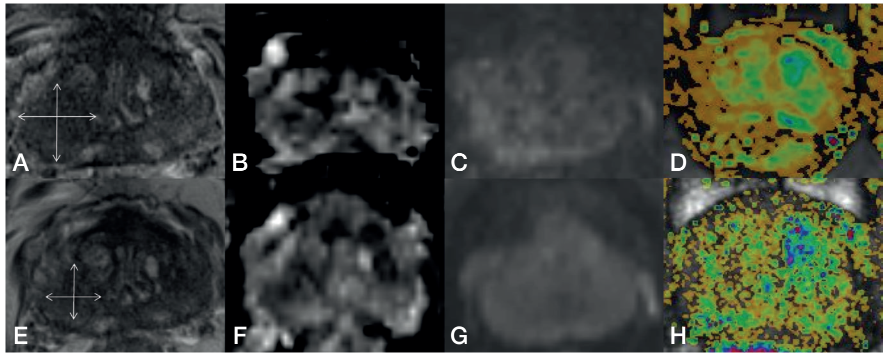
	PZ	TZ	PZ/TZ	Total
GS = 3+3	8	7	5	20
GS ≥ 3+4	7	5	1	13
No PCa	16	8	6	30
Total	31	20	12	63

GS = Gleason score; PCa = prostate cancer; PZ = peripheral zone; TZ = transition zone; PZ/TZ = lesions covering both the PZ and the TZ.

In two patients, csPCa was detected (GS 4+5 and 3+5) at repeat biopsy, while the volume of the lesion decreased between MRGB-1 and MRGB-2. In both patients, two radiologists agreed on the accuracy of MRGB-1 hitting the lesion properly. Figure 2-5 are examples of patients with csPCa findings at repeat biopsy.
Characteristics of positive lesions on MRGB-2

At initial mpMRI, 32 lesions scored PI-RADS 2 after consulting the third reader. Five lesions scored PI-RADS 3. PI-RADS 4 was scored in 19 patients. The remaining 7 patients scored PI-RADS 5 at initial mpMRI. Detection rates for csPCa was 19% (6/32) in PI-RADS 2, 20% (1/5) in PI-RADS 3, 11% (2/19) in PI-RADS 4 and 57% (4/7) in PI-RADS 5, respectively. Any PCa was detected in 41% (13/32), 80% (4/5), 53% (10/19) and 86% (6/7) in PI-RADS 2, 3, 4 and 5, respectively

Figure 2 A 68 years old patient with a PSA of 9.9 ng/ml having an mpMRI-1 and subsequent MRGB-1 of a lesion which was retrospectively scored PI-RADS 2 (A -D)



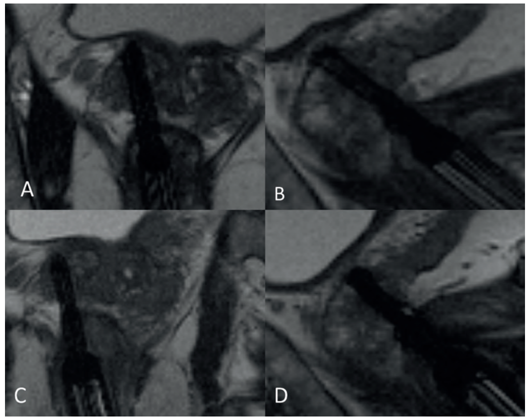
The maximal lesion diameter was 15 mm. After 11 months, his PSA increased to 12.6 ng/ml while the lesion volume decreased 0.23 ml. The maximum lesion diameter unchanged. At mpMRI-2, the lesion still scored PI-RADS 2 (E - H). During MRGB-2 (figure 3) a GS 3+5 csPCa was detected. A and E; axial T2 weighted images, B and F; calculated axial ADC map, C and G; axial Diffusion Weighted Images, D and H; color map representing Dynamic Contrast Enhancement images.
PSA = prostate specific antigen; mpMRI = multiparametric magnetic resonance imaging; MRGB = magnetic resonance imaging guided biopsy; PI-RADS = Prostate Imaging - Reporting and Data System GS = Gleason score; csPCa = clinically significant prostate cancer

A moderate interobserver agreement between both radiologists for the PI-RADS classification for lesions at mpMRI was reached with a weighted kappa value of 0.57 (95% confidence interval [CI], 0.36-0.78). In none of the patients with a decreasing PSA between MRGB-1 and MRGB-2, csPCa was detected (Figure 6). In patients with repeat biopsies, MRGB-1 was mostly performed in years 2010 and 2011 (n = 34) with 7 lesions resulting in csPCa at MRGB-2. MRGB-1 was never performed in year 2016 (Figure 7).

Follow up after negative MRGB-2

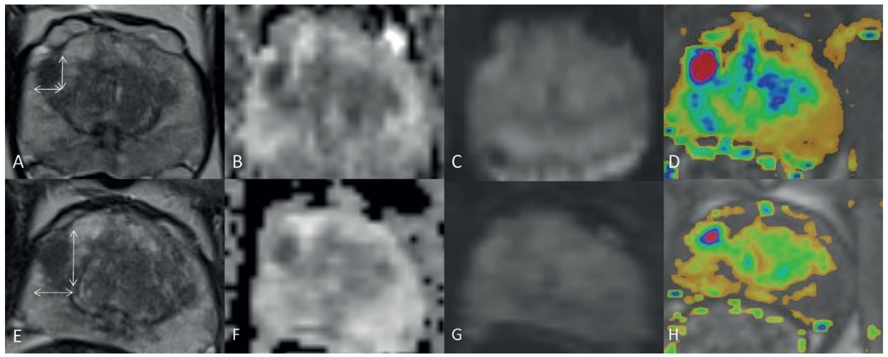
Three patients with negative MRGB-2 had another MRGB (hereafter , MRGB-3). In none of them PCa was detected. Their reassessed PI-RADS scores were PI-RADS 2, 4 and 5. In nine patients an mpMRI after MRGB-2 was obtained, those were assessed as being PI-RADS 2, no MRGB-3 was performed in those patients. In six patients no additional mpMRI was performed, because the PSA decreased after MRGB-2. In the remaining 45 patients, follow up data was not available.

Figure 3 Confirmation scan of the biopsy needle during MRGB of the patient represented in figure 2



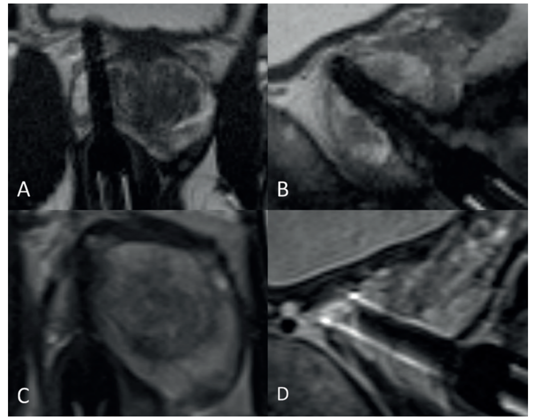
A and B are respectively axial and sagittal images of MRGB-1. C and D are respectively axial and sagittal images of MRGB-2. The needle was assumed to properly sample the lesion. MRGB = magnetic resonance imaging guided biopsy

Figure 4 A 52 years old patient with a PSA of 3.0 ng/ml having an mpMRI-1 and subsequent MRGB-1 of a lesion which was retrospectively scored PI-RADS 3 (A - D)



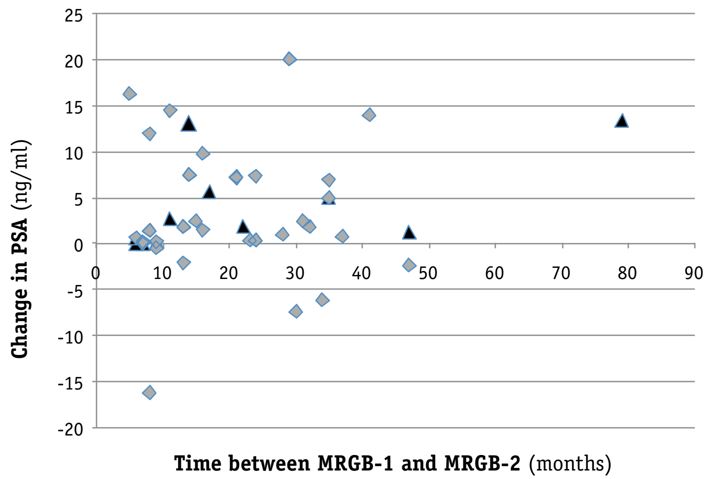
The maximal lesion diameter was 9 mm. After 17 months, his PSA increased to 8.6 ng/ml and the lesion volume increased 0.44 ml. The maximal lesion diameter increased to 13.5 mm. At mpMRI-2, the lesion scored PI-RADS 4 (E - H). During MRGB-2 (figure 5) GS 3+4 csPCa was detected. A A and E; axial T2 weighted images, B and F; calculated axial ADC map, C and G; axial Diffusion Weighted Images, D and H; color map representing Dynamic Contrast Enhancement images. PSA = prostate specific antigen; mpMRI = multiparametric magnetic resonance imaging; MRGB = magnetic resonance imaging guided biopsy; PI-RADS = Prostate Imaging - Reporting and Data System GS = Gleason score; csPCa = clinically significant prostate cancer

Figure 5 Confirmation scan of the biopsy needle during MRGB of the patient represented in figure 4



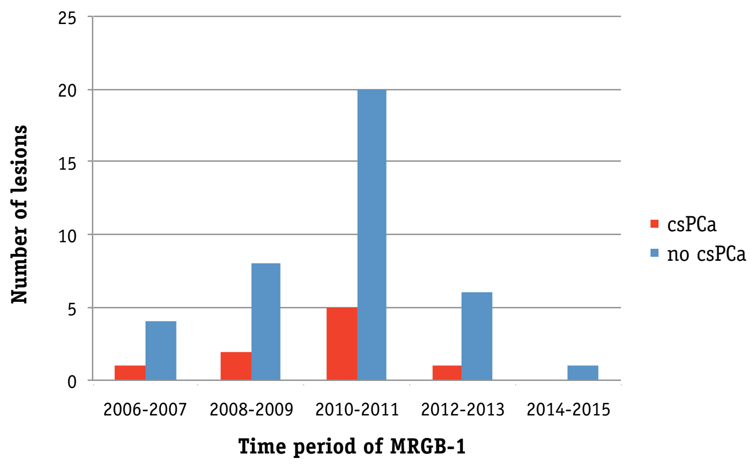
A and B are respectively axial and sagittal images of MRGB-1. C and D are respectively axial and sagittal images of MRGB-2. The needle was assumed to properly sample the lesion. MRGB = magnetic resonance imaging guided biopsy

Figure 6 Detection of csPCa correlated to the time between MRGB-1 and MRGB-2 and to the change in PSA



The triangles are representing the lesions with csPCa at MRGB-2 and the diamonds the lesions without csPCa at MRGB-2. PSA = prostate specific antigen; MRGB = magnetic resonance imaging guided biopsy; csPCa= clinically significant prostate cancer

Figure 7 Timing of MRGB-1 correlated to the number of lesions with csPCa detected during MRGB-2



In patients with repeat biopsy, MRGB-1 was never performed in 2016.
MRGB-1 = initial magnetic resonance imaging guided biopsy; csPCa= clinically significant prostate cancer

Discussion

To our knowledge, this study displayed the results of the first cohort of patients having repeat MRGB with negative first biopsies collected in more than ten years. We demonstrated that it might be beneficial to repeat the MRGB in case there is a continuing suspicion for having csPCa,, despite a negative first MRGB, as csPCa is detected in 21% of 75 lesions biopsied at MRGB-2. With a csPCa detection rate of again 21% (n = 13/63) for resampling the exact same lesion, we also demonstrated that it might be beneficial to target a lesion which was histologically proven to be negative on prior the MRGB.

With increasingly performed targeted biopsies, urologists are more often faced with patients with a suspicious lesion detected on mpMRI and a negative pathology outcome for that suspicious lesion. Yet, there is no guideline for follow up in such patients. Our study demonstrated that it might be beneficial for some patients to undergo rebiopsy such a lesion. This underlines the importance of follow up for some patients.

Studies about a repeat biopsy or surgery after MRI-TRUS fusion targeted biopsy show similar results. However, a head-to-head comparison is quite difficult due to the low number of patients in those and in our study. [12, 13] The lengthy time range of our study allows us to raise the question whether our findings still apply in today's practice. Therefore we reevaluated all biopsied lesions and we demonstrated that csPCa detection did not evidently change the course of the years in patients with repeat biopsy.

In retrospect, almost half of our cohort scored PI-RADS 2. This might be caused by an increase in experience we have in evaluating prostate MRI over the years. However, even within the cohort of patients with a reassessed PI-RADS 2, almost 19% (n=6/32) harbored csPCa at repeat biopsy. This is remarkable, as a comparable csPCa detection rate was seen in this study in patients with PI-RADS ≥ 3 (23%, 7/31). Moreover, detection rates for PI-RADS 4 and 5 described in the literature are quite higher. [17-20] This can have several causes, for example, the relatively small sample size of this study making a comparison of detection rates with those of other studies harder. Also, the lesions are already presampled making the yield of the rebiopsy poorer. Furthermore, involved radiologists may be biased by the knowledge that some of the biopsy results after MRGB-2 were positive for csPCa and that a first biopsy in the same lesion was negative. However, they were not aware of which and how many lesions were positive for csPCa. Also, the range of used mpMRI sequences might cause difficulties in the reassessment of the obtained images.

Intriguing are the two lesions with a decrease in volume and yet csPCa at repeat biopsy, as these findings are contrary to one's expectation. In both lesions, the radiologists rated the biopsies as accurate samplings of the lesions during MRGB-1. This can occur, for example, in case of surrounding tissue reaction which could be regressive in control scans and thus cause a false decrease in lesion diameter. [21] Further, we found that the time between MRGB-1 and MRGB-2 and PSA changes does not seems to influence the biopsy outcome of MRGB-2. Recommendations on timing of follow up in patients with change in PSA are therefore not possible. It appears that a rise in PSA, even a rapid increase in a relatively short period, seems not to be very helpful in selecting patients who will benefit from repeat biopsy. In an important amount of patients in our cohort with a rapid increase in PSA, csPCa was not detected during MRGB-2. On the other hand, none of the patients with a decreasing PSA had csPCa when resampling the same lesion. Also, timing of MRGB-1 does not seem to influence the results. The total number of performed MRGB-1 was highest in years 2010 and 2011, and also MRGB-1 of lesions resulting in csPCa at MRGB-2 was mostly performed within that time period. This might be explained by the fact that in our institution the total number of performed MRGBs was highest in that period.

One explanation for the detection of csPCa during MRGB-2 after a first session was negative may be the limitation of the biopsy technique. Although confirmation scans are made with the biopsy needle left in position, it remains difficult to assess the intralesional needle placement. Second, it may be explained by the biological progression. However, with a median time between MRGB-1 and MRGB-2 of 11 months in patients with positive MRGB-2, it is not very likely.

The most important limitation of our study was the long time range in which we included patients. Unfortunately, it was necessary to include a reasonable amount of patients. In a period of more than ten years, there are only 62 patients who had a repeat MRGB after an initial negative MRGB in our hospital. Unfortunately, doubling our sample size would thus probably have taken another ten years. Apparently, urologists and patients are not inclined to have another MRGB after the first one was negative. This can be well explained by the additional patient burden, the costs and the lower probability to detect a csPCa at repeat biopsy. A limitation of this large time span is the introduction of a learning curve. Nowadays, we have a lot more experience in both mpMRI readings and targeted biopsiescompared to ten years ago. Several studies showed the importance of experience in prostate MR reading and the method of biopsy acquisition.[7, 22] To minimize this limitation, we reassessed all lesions according to PI-RADS version 2. Also, we assessed whether the biopsy needle accurately targeted the suspicious lesion. Due to the small sample size, we were not able to provide predictors for a positive repeat MRGB. Further, selection bias will be introduced in this study as we only chose resampled lesions. Included patients were rebiopsied, because there was some reason to believe that patients had csPCa regardless of the negative findings during initial MRGB.

Also, a recurring limitation of all biopsy accuracy studies is the lack of a gold standard, for example, transperineal template prostate mapping or final radical prostatectomy. It would be extremely interesting to know whether a negative biopsy outcome is truly negative. Also, we only performed targeted biopsy without an additional systematic biopsy. As some studies reported csPCa detection rates(up to 10%) using systematic biopsy, which would be missed in a targeted only approach. Some advocate to perform systematic biopsy in addition to targeted biopsy.[1, 22, 23] Nonetheless, this study was only focusing on the yield of repeat targeted biopsy. It solely provides information on the utility of targeting a lesion again while it was negative for PCa on previous targeted biopsy. We hereby accept the chance that when we missed a lesion during the first biopsy, we might miss it again during repeat biopsy. In our institution, we try to minimize this chance by targeting each suspicious lesion at least twice. This approach, however, is debated as Schimmöller and colleagues demonstrated that there is limited benefit of targeting a lesion twice in the same session.[24]

Based on our results, taking the limitations into consideration, we can conclude that an important amount of patients might benefit from repeat biopsy after a negative MRGB. Disagreement between mpMRI lesion characteristics and the pathology should be evaluated carefully. Based on this study we cannot suggest which patients will benefit. Therefore, further study is warranted to establish predictors for a positive repeat targeted biopsy.

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6

Elastic versus rigid image registration in magnetic resonance imaging-transrectal ultrasound fusion prostate biopsy: a systematic review and meta-analysis

(European Urology Focus, 2018)

Venderink W, de Rooij M, Sedelaar JPM, Huisman HJ, Futterer JJ

Abstract

Context The main difference between the available Magnetic Resonance Imaging (MRI) – Transrectal Ultrasound (TRUS) fusion platforms for prostate biopsy is the method of image registration being either rigid or elastic. As elastic registration compensates for possible deformation, caused by the introduction of a ultrasound probe for example, it is expected that it would perform better than rigid registration.

Objective The aim of this meta-analysis is to compare rigid with elastic registration by calculating for both subgroups the detection odds ratio (OR). The detection OR is defined as the ratio of the odds of detecting clinically significant prostate cancer (csPCa) by MRI-TRUS fusion biopsy compared to systematic TRUS biopsy. Secondary objectives were OR for any PCa and the OR after pooling both registration techniques.

Evidence acquisition The electronic databases Pubmed, Embase and Cochrane were systematically searched for relevant studies according to the Preferred Reporting Items for Systematic Review and Meta-analysis Statement. Studies comparing MRI-TRUS fusion and systematic TRUS guided biopsies in the same patient were included. The quality assessment of included studies was performed using the Quality Assessment of Diagnostic Accuracy Studies version 2.

Evidence synthesis Eleven papers describing elastic and ten describing rigid registration were included. Meta-analysis showed an OR of csPCa for elastic and rigid registration of 1.45 (95% CI, 1.21-1.73; $p < 0.0001$) and 1.40 (95% CI, 1.13-1.75; $p = 0.002$) respectively. No significant difference was seen between the subgroups ($p = 0.83$). Pooling subgroups resulted in a OR of 1.43 (95% CI, 1.25-1.63; $p < 0.00001$).

Conclusions No significant difference is identified between rigid and elastic registration for MRI-TRUS fusion guided biopsy in the detection of csPCa while both techniques detect more csPCa than TRUS-guided biopsy.

Introduction

Prostate cancer (PCa) is the most common malignancy among Western men and it is the second leading cause of cancer-related mortality.[1] Measurement of serum prostate specific antigen (PSA) and a digital rectal exam (DRE) are the first steps in PCa diagnoses. The pathologic evaluation of 10-12 core systematic transrectal ultrasound (TRUS) guided biopsies of the prostate is the standard to confirm the diagnosis.[2] Unfortunately, TRUS guided biopsy is prone to random and systematic error and it is associated with several problems, for example overdiagnosis of insignificant cancer and underdiagnosis of significant cancer.[3]

Recently, multiparametric (mp) Magnetic Resonance Imaging (MRI) has been introduced for the detection and localization of PCa. mpMRI allows for accurate assessment of the prostate and it can improve the diagnostic pathway of PCa. Despite the accurate assessment of mpMRI, pathologic confirmation of obtained biopsies remains the gold standard to finally objectify PCa and assess the aggressiveness. However, mpMRI can be used for direct in-bore or MRI-TRUS fusion guided biopsy. MRI-TRUS fusion guided biopsy can be divided into cognitive and software assisted fusion. In the latter procedure the prostate is visualized in real-time using TRUS and the location of the tumor, annotated in the pre-biopsy mpMRI, is registered to these ultrasound images with the use of software. Both direct in-bore targeted biopsy studies and software assisted MRI-TRUS fusion biopsy studies have shown promising results in the detection of PCa.[4-7]

Software assisted MRI-TRUS fusion guided biopsy is less expensive and more readily available compared to direct in-bore biopsy and it is therefore most used to target suspected lesions seen on mpMRI. Software assisted MRI-TRUS fusion is offered by various commercially available platforms, each with its own specific features. The main difference between the platforms is the type of image registration being either rigid or non-rigid (elastic). Rigid image registration overlays the mpMRI images onto the TRUS images during the biopsy procedure without adjustment for possible deformation of the prostate due to patient movement or the introduction of the TRUS probe.[8,9] Elastic registration on the other hand tries to compensate for this deformation and it is therefore expected that it would be more accurate than rigid image registration.[10-12] The aim of this systematic review and meta-analysis is to compare the detection rates of clinically significant (cs)PCa between rigid MRI-TRUS fusion and elastic MRI-TRUS fusion.

Evidence acquisition

Search strategy

The electronic databases Pubmed, Embase and Cochrane were systematically searched for relevant studies. No limitations on language or date were used. The following search term was used: ("magnetic resonance imaging" or "MRI" or "MR" or "NMR" or "mpMRI" or "ultrasonography" or "US" or "MR-TRUS" or "MR-US" or "MR/US") AND ("fusion" or "registration" or "targeted" or "target" or "software") AND ("prostate" or "prostatecancer" or "prostatic neoplasm" or "PCA" or "cancer") AND ("detection" or "rate" or "utility" or "yield" or "efficiency" or "results"). Reference lists and two recent review articles were searched for missed eligible articles.[4,13] The last search was performed on July 7, 2015. All studies were imported into Endnote (version X7.2, Thomson Reuters). This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[14]

Study selection and data extraction

One reviewer (W.V.) performed the study selection and data extraction. A first eligibility assessment was performed based on title and abstract screening. The remaining articles were selected after full text assessment. Conference abstracts were not included. Only studies comparing software assisted MRI-TRUS fusion and systematic TRUS guided biopsies in the same patient were included.

The main outcome measure was the detection rate of csPCa. The definition of clinically significance elected in the original report was used in this review. So, different definitions of clinically significance were used. The secondary outcome measure was the detection rate of any PCa.

A data extraction form was used to extract the following data: study, population, MRI and biopsy characteristics. The detection rates were calculated from the published data.

Quality assessment

The quality assessment of the included studies was performed by two reviewers [W.V. and M. de R.] using the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2).[15] Disagreements were resolved by consensus. The two reviewers were not blinded during this quality assessment. The signaling questions of domain 2 (Index Test(s)) and domain 4 (Flow and timing) were adjusted so that the quality assessment fit our research question. Domain 2 includes the signaling questions: 1) Is the systematic biopsy operator blinded for the location of the lesion found on mpMRI and 2) Was it clear at which threshold patients underwent targeted biopsy. Domain 4 includes the signaling questions: 1) Was an appropriate time interval used between mpMRI and biopsy, 2) Was targeted biopsy performed prior to systematic biopsy, 3) Underwent all patients the same biopsy procedure and 4) Were all patients included in the analysis.

Data synthesis and analysis

We calculated the detection rates for each study of both csPCa and any PCa. To compare the elastic and rigid registration methods two subgroups were made. The detection rate was defined as the proportion of men in which (cs)PCa was detected divided by the number of men in the entire cohort.

Detection odds ratios (OR) were calculated and compared using Review Manager (version 5.3).[16] The OR is the ratio of the odds that (cs)PCa will be detected to the odds that it will not be detected with targeted biopsy compared to systematic biopsy. As we expect heterogeneity between the included studies a random-effects model was used. Significance of the overall OR and the OR of each subgroup was determined using a Z-test. To determine significant differences between the OR of the two subgroups a Chi2-test was used. To illustrate any heterogeneity of the results, the OR's of the different studies are displayed using forest plots. The I2 statistic was used to quantify heterogeneity. An I2 below 40% indicates no substantial heterogeneity.

Evidence synthesis

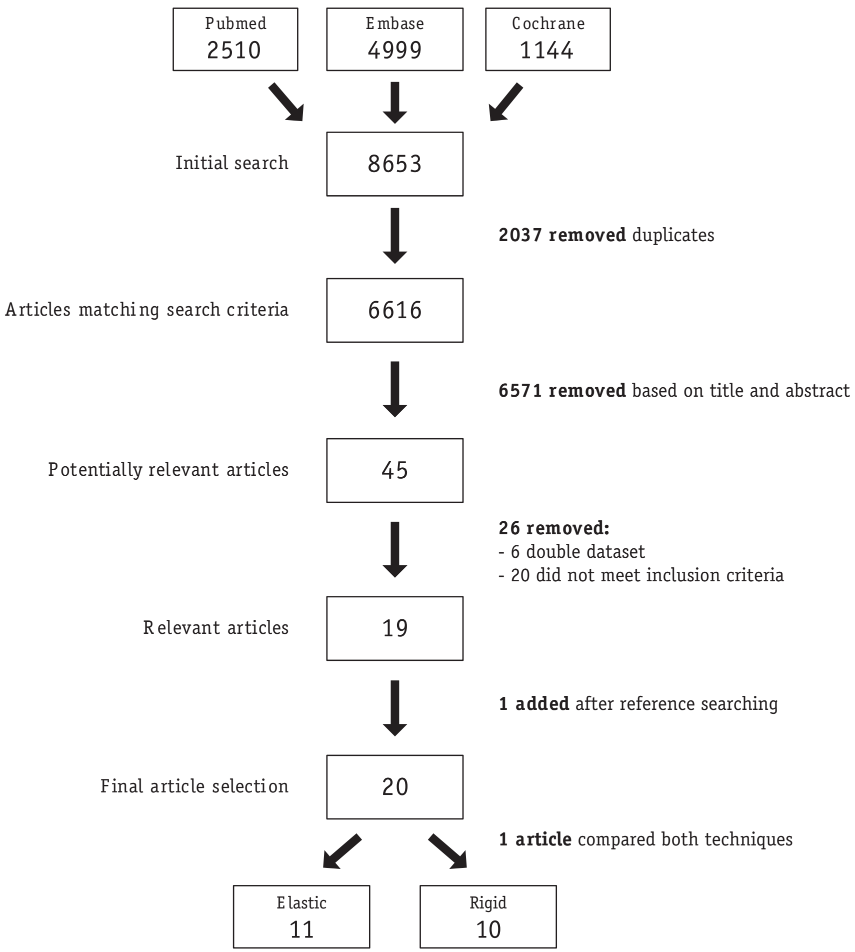
Literature search and study selection

Figure 1 shows an overview of the literature search and the study selection. The search yielded 8653 records, 6616 records left after removing duplicates. Based on screening title and abstract 45 articles remained. After removing articles using the same dataset and removing articles not fulfilling the inclusion criteria 19 relevant articles remained. One article was added after cross-reference searching which resulted in 20 included relevant articles.

Study and patient characteristics

Supplementary table 1 summarizes the study, population, MRI and biopsy characteristics of the included studies. Eleven papers using elastic image registration [9,17-26] and ten papers using rigid image registration finally left.[9,27-35] As one paper compared both techniques, it was included in both subgroups. The subgroup using elastic registration comprised 1598 men, the rigid registration subgroup 2318. In four studies the detection rate of csPCa could not be measured [24,29-31] and in one study the detection rate of any PCa could not be measured.[18]

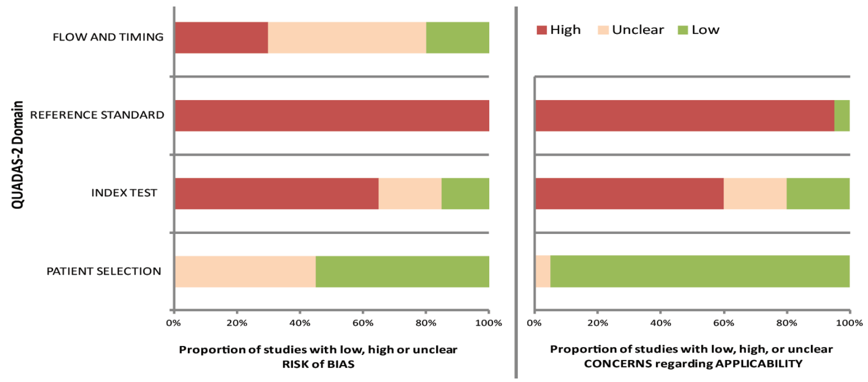
Figure 1 Chart showing the results of the literature search



Quality assessment

The results of the quality assessment are depicted in figure 2 and supplementary figure 1. The risk of bias regarding patient selection was unclear in nine studies.[18,20,28,29,31-35] The unclear risk was mainly caused by a lack of data on patient enrollment or patient exclusion. The risk of bias concerning the index test was low in three studies as these studies explicitly reported the operator of systematic biopsies was blinded for the target lesion.[19,29,35] The concerns about applicability regarding the reference test scored high in all studies except for one as all studies used systematic TRUS guided biopsy as inadequate reference test.

Figure 2 Methodologic quality overview of risk of bias and concerns regarding applicability of the 20 studies included in this systematic review using Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)



Only one study used transperineal template saturation biopsy.[32] The risk of bias regarding flow and timing was low in four studies.[18,25,28,34] Five studies mentioned an appropriate time interval between MRI and the biopsy procedure.[18,20,25,28,34] Some studies performed a systematic biopsy prior to targeted biopsy.[9,19,20,23,26,32]

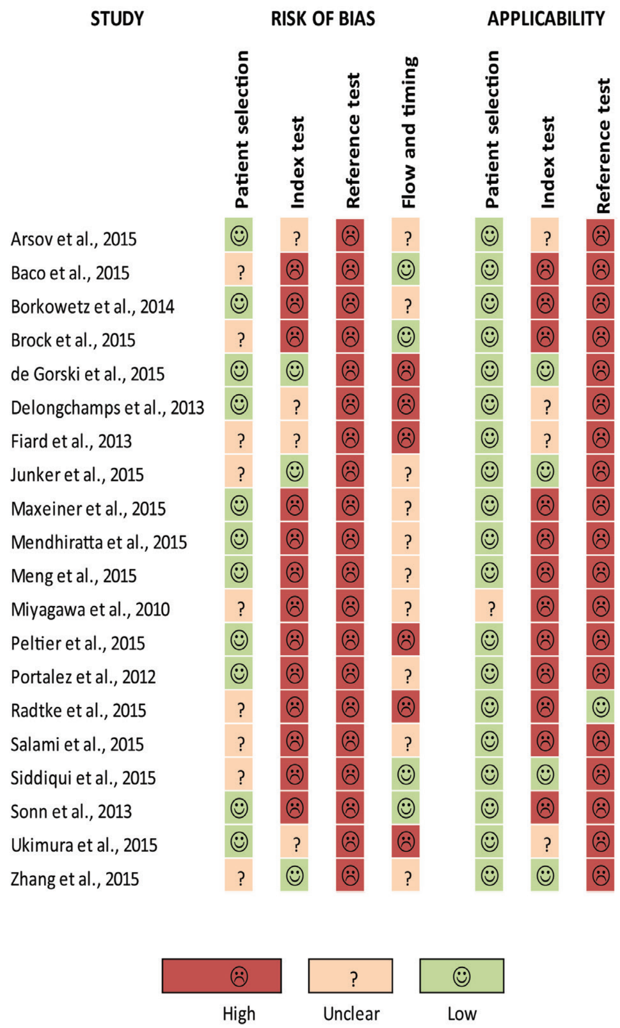
Clinically significant prostate cancer

The detection rates for the individual studies are displayed in table 1. The OR for csPCa was 1.45 (95% CI, 1.21-1.73; $p < 0.0001$) and 1.40 (95% CI, 1.13-1.75; $p = 0.002$) for the elastic and the rigid registration subgroup respectively both in favor of targeted biopsy. No significant difference was seen between the subgroups ($p = 0.83$). Figure 3 shows a forest plot to illustrate heterogeneity. I2 was 9% for the elastic and 39% for the rigid subgroup.

The median detection rate of csPCa in the elastic registration subgroup was 34.59 (IQR, 20.30-43.97) and 25.34 (IQR, 14.29-36.05) for targeted and systematic biopsy respectively. The median detection rate of csPCa in the rigid registration subgroup was 25.19 (IQR, 22.58-35.74) and 23.13 (IQR, 12.16-28.52) for targeted and systematic biopsy respectively.

Pooling both subgroups resulted in an OR of 1.43 (95% CI, 1.25-1.63; $p < 0.00001$) in favor of targeted biopsy with an I2 of 19%. The median for targeted biopsy was 25.96 (IQR, 21.44-43.25) and for systematic biopsy 25.00 (IQR, 14.06-29.90). The funnel plot depicted in supplementary figure 2 is symmetric so there appears to be no presence of publication bias.

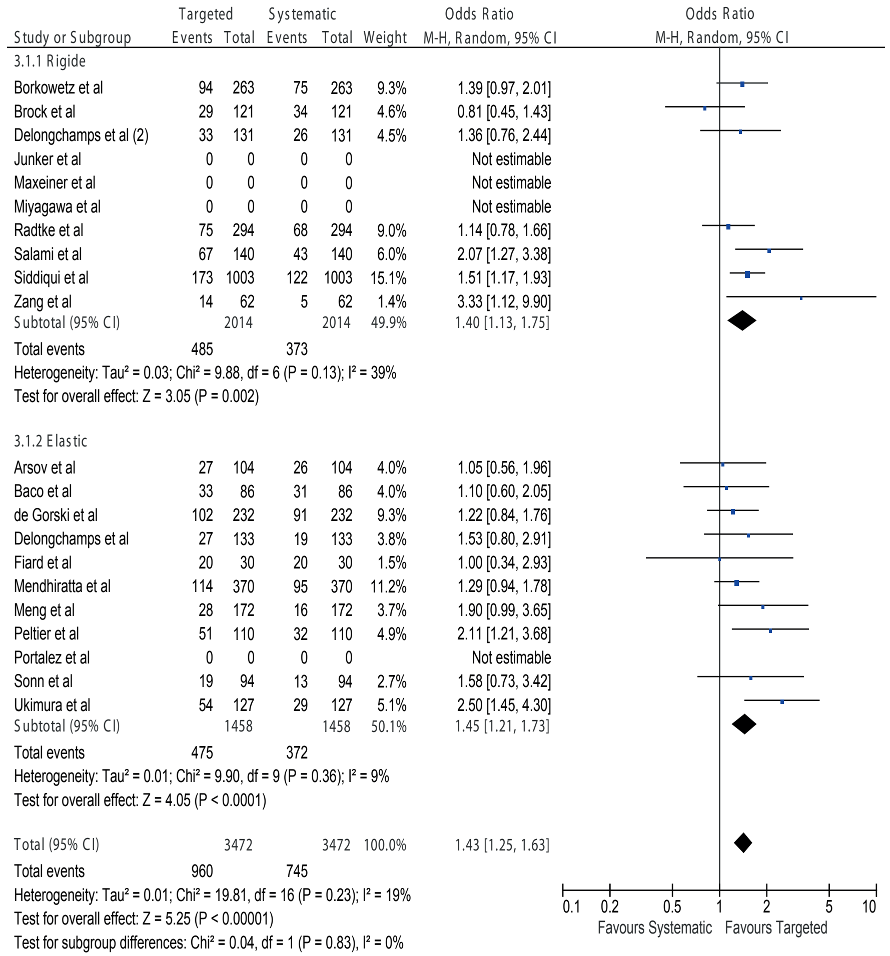
Supplementary figure 1 Methodologic quality assessment using Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) of each individual study



Any prostate cancer

The OR of any PCa was 1.28 (95% CI, 0.97-1.71; p = 0.09) and 1.01 (95% CI, 0.80-1.27; p = 0.94) in the elastic and the rigid registration subgroup respectively both in favor of targeted biopsy. There is no significant difference between the subgroups (p = 0.19). Figure 4 shows a forest plot to illustrate heterogeneity. I2 was 69% and 64% in the elastic and the rigid subgroup respectively.

Figure 3 Forrest plots showing results of the meta-analysis of included studies reporting the detection rate of clinically significant prostate cancer (csPCa) detected by magnetic resonance imaging (MRI)- transrectal ultrasound (TRUS) fusion guided biopsy versus systematic TRUS guided biopsy



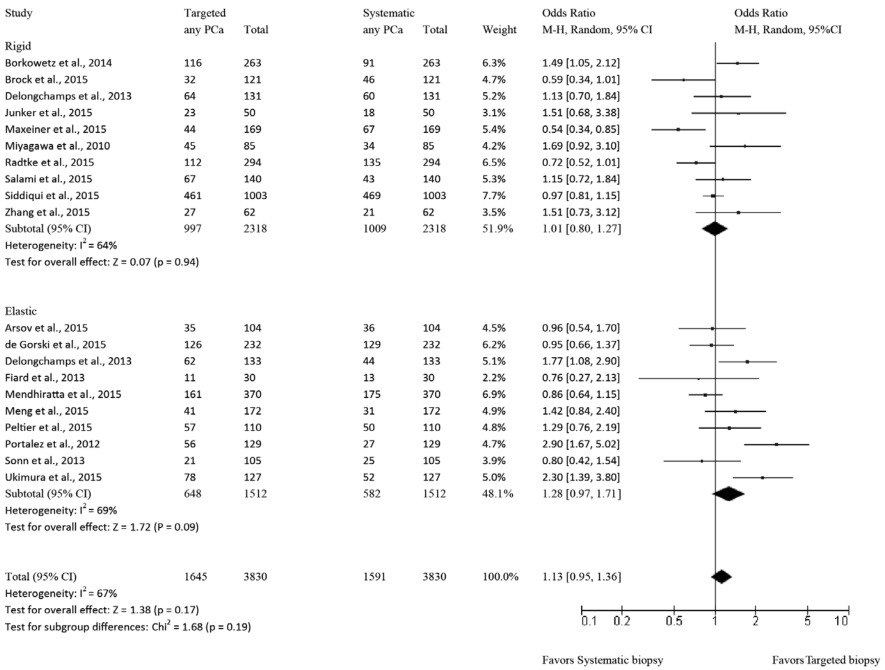
The *squares* indicate the mean, the *whiskers* indicate the 95% CI. The *diamonds* indicate the pooled estimate. M-H_2 = Mantel- Haenszel method for random-effects.

Table 1 Detection rates of targeted and systematic biopsy of the included studies

				Detection rate							
				Targeted biopsy				Systematic biopsy			
		Included patients		csPCa		any PCa		csPCa		any PCa	
Study	Definition csPCa	Entire cohort	No. of patients with a target lesion	Entire cohort (%)	Part of cohort with target lesion (%)	Entire cohort (%)	Part of cohort with target lesion (%)	Entire cohort (%)	Part of cohort with a target lesion (%)	Entire cohort (%)	Part of cohort with target lesion (%)
Arsov	Gleason ≥3+4	104	104	-	26.0	-	33.7	-	25.0	-	34.6
Baco	Gleason ≥3+4 or cancer core length ≥5mm	86	63	38.4	52.4	N.A.	N.A.	36.0	44.4	N.A.	N.A.
de Gorski	Gleason ≥ 3+4 or cancer core length ≥4mm	232	232	-	44.0	-	54.3	-	39.2	-	55.6
Delongchamps	Gleason ≥3+4	133	82	20.3	32.9	46.6	75.6	14.3	N.A.	33.1	N.A.
Fiard	Gleason ≥ 3+4 or cancer core length ≥10mm	30	20	33.3	50.0	36.7	55.0	33.3	45.0	43.3	50.0
Mendhiratta	Gleason ≥3+4	370	370	-	30.8	-	43.5	-	25.7	-	47.3
Meng	Gleason ≥3+4	172	172	-	16.3	-	23.8	-	9.3	-	18.0
Peltier	Gleason ≥ 3+4 or cancer core length ≥6mm[1]	110	100	46.4	51.0	51.8	57.0	29.1	N.A.	45.5	N.A.
Portalez	Gleason ≥3+4	129	129	-	N.A.	-	43.4	-	N.A.	-	20.9
Sonn	Gleason ≥ 3+4 or cancer core length ≥4mm	94	94	-	20.2	-	22.3	-	13.8	-	26.6
Ukimura	Gleason ≥ 3+4 or cancer core length ≥5mm	127	127	-	42.5	-	61.4	-	22.8	-	40.9
Borkowetz	Epstein	263	263	-	35.7	-	44.1	-	28.5	-	34.6
Brock	Epstein	121	114	24.0	25.4	26.4	28.1	28.1	28.9	38.0	38.6
Delongchamps	Gleason ≥3+4	131	78	25.2	42.3	48.9	82.1	19.8	N.A.	45.8	N.A.
Junker	N.A.	50	50	N.A.	N.A.	-	46.0	N.A.	N.A.	36.0	-
Maxeiner	N.A.	169	169	N.A.	N.A.	-	26	N.A.	N.A.	-	39.6
Miyagawa	N.A.	85	85	N.A.	N.A.	-	52.9	N.A.	N.A.	-	40.0
Radtke	Gleason ≥3+4	294	196	25.5	38.3	38.1	57.1	23.1	34.7	45.9	68.9
Salami	Epstein	140	140	-	47.9	-	52.1	-	30.7	-	48.6
Siddiqui	Gleason ≥4+3	1003	1003	-	17.2	-	46.0	-	12.2	-	46.8
Zhang	Gleason ≥3+4 high volume[1]	62	62	-	22.6	-	43.5	-	8.1	-	33.9

csPCa = clinically significant prostate cancer
The definition for csPCa in systematic biopsy is the same as for targeted but in systematic biopsy Gleason 6 in ≥ 3 cores is also considered csPCA.

Figure 4 Forrest plots showing results of the meta-analysis of included studies reporting the detection rate of any prostate cancer (PCa) detected by magnetic resonance imaging (MRI)- transrectal ultrasound (TRUS) fusion guided biopsy versus systematic TRUS guided biopsy



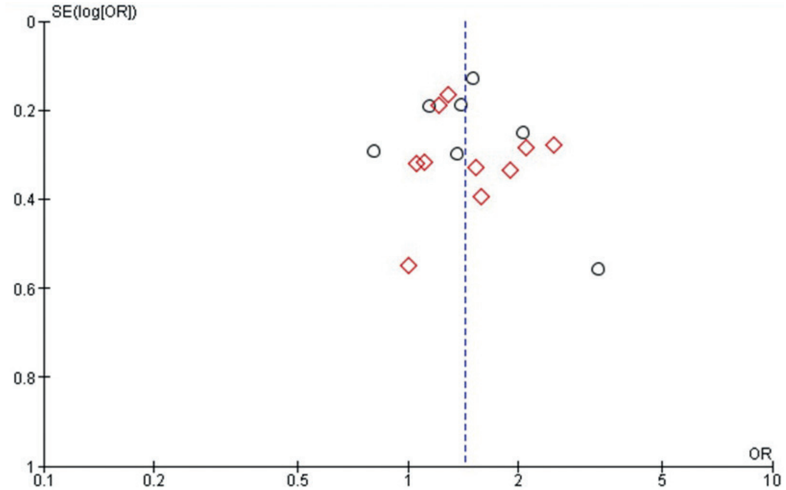
Study	Targeted any PCa	Targeted Total	Systematic any PCa	Systematic Total	Weight	Odds Ratio M-H, Random, 95% CI
Rigid						
Borkowetz et al., 2014	116	263	91	263	6.3%	1.49 [1.05, 2.12]
Brock et al., 2015	32	121	46	121	4.7%	0.59 [0.34, 1.01]
Delongchamps et al., 2013	64	131	60	131	5.2%	1.13 [0.70, 1.84]
Junker et al., 2015	23	50	18	50	3.1%	1.51 [0.68, 3.38]
Maxeiner et al., 2015	44	169	67	169	5.4%	0.54 [0.34, 0.85]
Miyagawa et al., 2010	45	85	34	85	4.2%	1.69 [0.92, 3.10]
Radtke et al., 2015	112	294	135	294	6.5%	0.72 [0.52, 1.01]
Salami et al., 2015	67	140	43	140	5.3%	1.15 [0.72, 1.84]
Siddiqui et al., 2015	461	1003	469	1003	7.7%	0.97 [0.81, 1.15]
Zhang et al., 2015	27	62	21	62	3.5%	1.51 [0.73, 3.12]
Subtotal (95% CI)	997	2318	1009	2318	51.9%	1.01 [0.80, 1.27]
Heterogeneity: I^2 = 64%						
Test for overall effect: Z = 0.07 (p = 0.94)						
Elastic						
Arsov et al., 2015	35	104	36	104	4.5%	0.96 [0.54, 1.70]
de Gorski et al., 2015	126	232	129	232	6.2%	0.95 [0.66, 1.37]
Delongchamps et al., 2013	62	133	44	133	5.1%	1.77 [1.08, 2.90]
Fiard et al., 2013	11	30	13	30	2.2%	0.76 [0.27, 2.13]
Mendhiratta et al., 2015	161	370	175	370	6.9%	0.86 [0.64, 1.15]
Meng et al., 2015	41	172	31	172	4.9%	1.42 [0.84, 2.40]
Peltier et al., 2015	57	110	50	110	4.8%	1.29 [0.76, 2.19]
Portalez et al., 2012	56	129	27	129	4.7%	2.90 [1.67, 5.02]
Sonn et al., 2013	21	105	25	105	3.9%	0.80 [0.42, 1.54]
Ukimura et al., 2015	78	127	52	127	5.0%	2.30 [1.39, 3.80]
Subtotal (95% CI)	648	1512	582	1512	48.1%	1.28 [0.97, 1.71]
Heterogeneity: I^2 = 69%						
Test for overall effect: Z = 1.72 (P = 0.09)						
Total (95% CI)	1645	3830	1591	3830	100.0%	1.13 [0.95, 1.36]
Heterogeneity: I^2 = 67%						
Test for overall effect: Z = 1.38 (p = 0.17)						
Test for subgroup differences: Chi^2 = 1.68 (p = 0.19)						

The squares indicate the mean, the whiskers indicate the 95% CI. The diamonds indicate the pooled estimate. M-H2 = Mantel- Haenszel method for random-effects.

The median detection rate of PCa in the elastic registration subgroup was 43.46 (IQR, 33.65-51.82) and 37.78 (IQR, 23.81-45.45) for targeted and systematic biopsy respectively. The median detection rate of any PCa in the rigid registration subgroup was 45.04 (IQR, 38.10-48.85) and 39.82 (IQR, 36.00-45.92) for targeted and systematic biopsy respectively.

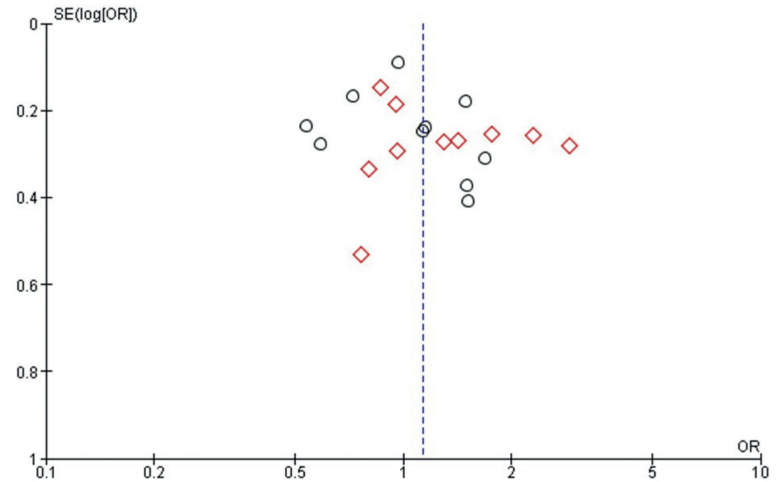
Pooling both subgroups resulted in an OR of 1.13 (95% CI, 0.95-1.36; p = 0.17) in favor of targeted biopsy with an I2 of 67%. The median for targeted biopsy was 43.83 (IQR, 35.16-50.34) and for systematic biopsy 39.82 (IQR, 34.24-45.86). The funnel plot depicted in supplementary figure 3 is symmetric so there appears to be no presence of publication bias.

Supplementary figure 2 Funnel plot for clinically significant prostate cancer



The *circles* indicate the studies regarding the rigid image registration and the *squares* indicate the studies regarding the elastic image registration.

Supplementary figure 3 Funnel plot for any prostate cancer



The circles indicate the studies regarding the rigid image registration and the squares indicate the studies regarding the elastic image registration.

Supplementary table 1

Study		Population					MRI					Biopsy					
Author	**Design**	**Patients used in analysis**	**Biopsy history**	**Age (years)**	**PSA (ng/ml)**	**Prostate volume (cc)**	**Magnetic field strength (T)**	**mpMRI Sequences**	**Endo-rectal coil**	**Score**	**Biopsy threshold**	**Patients biopsied (%)**	**Fusion platform (registration)**	**Route**	**Standard test**	**Targeted biopsy first**	**No. of targeted cores per patient**
Arsov et al., 2015	Prospective	104[1]	Prior negative biopsy	Median 68 (IQR 63-71)	Median 10.8 (IQR 7.4-15.5)	Median 60 (IQR 42-82)	3	T2, DWI,DCE	N	5-point and PI-RADS	Sumscore ≥ 10 out of 15	104 (100)	Urostation (elastic)	TR	TR 12-core	Y	Mean 5.4
Baco et al., 2015	Prospective	86[1]	Initial biopsy	Median 64 (IQR 58-69)	Median 6.9 (IQR 5.2-9.2)	Median 45 (IQR 33-60)	1.5	T2, DWI	N	5-point	≥3	63 (73.3)	Urostation (elastic)	TR	TR 12-core	Y	Median 2
de Gorski et al., 2015	Prospective	232	Initial biopsy	Mean 64 (SD ± 6.4)	Mean 6.5 (SD ± 1.8)	Mean 47 (SD ± 24.3)	1.5	T2, DWI, DCE	N	5-point	≥2	232 (100)	Urostation (elastic)	TR	TR 12-core	N	Median 2
Delongchamps et al., 2013	Prospective	133[2]	Initial biopsy	Mean 64.5 (SD ± 7.9)	Mean 9 (SD ± 3.9)	Mean 58.3 (SD ± 28.6)	1.5	T2, DWI, DCE	Y	3-point	≥2	82 (61.7)	Urostation (elastic)	TR	TR 10-12 core	N	Median 3
Fiard et al., 2013	Prospective	30	Prior negative biopsy (17) Initial biopsy (13)	Median 64 (range 61-67)	Median 6.3 (range 5.2-8.8)	Median 46 (range 31-59)	3	T2, DWI, DCE	N	PI-RADS	Sumscore ≥ 5 out of 15	20 (66.7)	Urostation (elastic)	TR	TR 12-core	N	Median 2
Mendhiratta et al., 2015	Retrospective	370	Initial biopsy	Mean 64.6 (SD ± 8.5)	Mean 6.8 (SD ± 0.3)	Median (46 (IQR 36-62)	3	T2, DWI, DCE	N	5-point	≥2	370 (100)	Artemis (elastic)	TR	TR 12-core	Y	Mean 5.7
Meng et al., 2015	Retrospective	172[1]	Prior negative	Mean 65.9 (SD ± 7.5)	Mean 8.9 (SD ± 0.7)	Mean 76.9 (SD ± 44.4)	3	T2, DWI, DCE	N	5-point	≥2	172 (100)	Artemis (elastic)	TR	TR 12-core	Y	N.A.
Peltier et al., 2015	Prospective	110	Initial biopsy	Median 65.8 (IQR 59.5-70.7)	Median 6.9 (IQR 4.6-9.6)	Median 44 (IQR 35-59)	3	T2, DWI,DCE	Y	3-point	None	110 (100)	Urostation (elastic)	TR	TR 12-core	N	Median 2.4
Portalez et al., 2012	Prospective	129	Prior negative biopsy	Mean 64.7 (range 47-79)	Mean 9.6 (range 2.7-40)	Mean 51.1 (range 12-192)	1.5	T2, DWI, DCE	Y	5-point	N.A.	129 (100)	Urostation (elastic)	TR	TR 12-core	Y	Mean 3.1
Sonn et al., 2013	Prospective	94	Prior negative biopsy	Median 65 (IQR 59-70)	Median 7.5 (IQR 5.0-11.2)	Median 58 (IQR 39-82)	3	T2, DWI, DCE	N	5-point	≥2	94 (100)	Artemis (elastic)	TR	TR 12-core	Y	Mean 5.46
Ukimura et al., 2015	Retrospective	127	Prior negative biopsy (70) Initial biopsy (57)	Median 66 (range 39-81)	Median 5.8 (range 1.4-28.8)	N.A.	3	T2, DWI, DCE	N	3-point	≥2	127 (100)	Urostation (elastic)	TR	TR 10-12 core	N	Mean 2.78
Borkowetz et al., 2014	Retrospective	263	Prior negative biopsy (195) Initial biopsy (68)	Median 66 (range 47-83)	Median 8.3 (range 0.4-86.6)	Median 50 (range 12-220)	3	T2, DWI,DCE	N	PI-RADS	≥2	263 (100)	Biojet (rigid)	TP	TR 12-core	Y	Mean 8.9
Brock et al., 2015	Prospective	121	Prior negative biopsy	Mean 64 (SD ± 6.6)	Mean 11.7 (SD ± 7.0)	Mean 64.6 (SD ± 32.1)	3	T2,DWI, DCE	N	PI-RADS	N.A.	114 (94.2)	HI-VISION (rigid)	TR	TR 12-core	Y	Mean 2.8
Delongchamps et al., 2013	Prospective	131[2]	Initial biopsy	Mean 64.6 (SD ± 6.7)	Mean 8.3 (SD ± 4.1)	Mean 55.7 (SD ± 35.1)	1.5	T2, DWI, DCE	Y	3-point	≥2	78 (59.5)	Esaote (rigid)	TR	TR 10-12 core	N	Median 4
Junker et al., 2015	Prospective	50	Mixed (no. N.A.)	Mean 63.7 (SD ± 7.9)	Mean 7.6 (SD ± 4.2)	Mean 49.2 (SD ± 21.9)	3	T2, DWI. DCE	N	PI-RADS	≥3	50 (100)	Logic (rigid)	TR	TR 10-core	Y	Mean 4.5
Maxeiner et al., 2015	Prospective	169	Prior negative biopsy (151) Initial biopsy (18)	Mean 65.6 (SD ± 7.71)	Mean 13.9 (SD ± 13.7)	Mean 60.6 (SD ± 35.3)	3	T2, DWI	N	PI-RADS	N.A.	169 (100)	Aplio 500 (rigid)	TR	TR 10-core	Y	Mean 1.86
Miyagawa et al., 2010	Prospective	85	Prior negative biopsy	Median 69 (range 50-84)	Median 9.9 (range 4.0-34.2)	Median 37.2 (range 18-141)	1.5	T2, DWI, DCE	N	N.A.	N.A.	85 (100)	RVS (rigid)	TR	Combined TP and TR 10-11 cores	Y	Mean 2.3
Radtke et al., 2015	Prospective	294	Prior negative biopsy (108) Initial biopsy (186)	Median 64 (IQR 60-71)	Mean 7.3 (SD ± 6.0)	Mean 47 (SD ± 37.5)	3	T2, DWI, DCE	N	PI-RADS	≥2	196 (66.7)	BiopSee (rigid)	TP	TP template saturation biopsy (24-core)	N	Median 4

Supplementary table 1 Continued

Study		Population					MRI				Biopsy						
Author	Design	Patients used in analysis	Biopsy history	Age (years)	PSA (ng/ml)	Prostate volume (cc)	Magnetic field strength (T)	mpMRI Sequences	Endo-rectal coil	Score	Biopsy threshold	Patients biopsied (%)	Fusion platform (registration)	Route	Standard test	Targeted biopsy first	No. of targeted cores per patient
Salami et al., 2015	Prospective	140	Prior negative biopsy	Median A) 66.3 (IQR 61-72.8) B) 65.3 (IQR 60.3-68.2)[3]	Median A) 10.7 (IQR 6.9-16.5) B) 8.0 (IQR 5.4-11.2)[2]	Median A) 46.5 (IQR 35-61.6) B) 56 (IQR 40-70.8)[2]	3	T2, DWI, DCE	Y	5-point	≥2	140 (100)	Uronav (rigid)[4]	TR	TR 12-core	Y	2
Siddiqui et al., 2015	Prospective	1003	Prior negative biopsy (807) Initial biopsy (196)	Mean 62.1 (SD ± 7.5)	Median 6.7 (IQR 4.4-10.7)	Median 49 (IQR 36-71)	3	T2,DWI, DCE, Spectroscopy	Y	3-point	None	1003 (100)	Uronav (rigid)[4]	TR	TR 12-core	Y	Mean 5.3
Zhang et al., 2015	Prospective	62	Initial biopsy	Mean 68.4 (range 51-79)	Mean 10.2 (range 4.5-30.1)	Mean 34.1 (range 19-64)	3	T2, DWI,DCE	N	PI-RADS	≥2	62 (100)	RVS (rigid)	TP	TP	Y	Mean 4.2

Characteristics of included studies. PSA = prostate specific antigen; mp = multiparametric; MRI = magnetic resonance imaging; T2 = T2-weighted imaging; DWI = diffusion weighted imaging; DCE = dynamic contrast enhancement; PI-RADS = Prostate Imaging Reporting and Data System; TR = transrectal; N = no; Y = yes. [1] Patients included in this analysis were part of a wider study, only data relevant for this review was used. [2] The article both compared rigid and elastic image registration. [3] The article is dividing the cohort based on the final results in A) patients with clinically significant prostate cancer and B) patients with no PCa or indolent PCa. Uronav offers both a rigid and a elastic image registration option. In this paper the rigid image registration option was used.

Discussion

This systematic review did not identify significant differences in the detection rates of both any and csPCa between elastic image registration and rigid image registration for MRI-TRUS fusion guided biopsy while MRI-TRUS fusion guided biopsy as a whole detects more csPCa compared to TRUS guided biopsy. The results for any PCa did not differ between MRI-TRUS fusion and TRUS guided biopsy.

These findings can be explained by the fact that rigid registration requires a cognitive optimization of the registration; after rigid software assisted fusion the operator compensates cognitively for any prostate deformation.

The role of mpMRI in detecting and assessing aggressiveness of a tumor is increasingly being recognized and implemented in daily practice.[36-38] As a consequence MRI-targeted biopsies are more and more being performed, both direct in-bore as MRI-TRUS fusion guided biopsy. Many studies reported higher or similar rates of csPCa detection whilst lower rates of clinically insignificant PCa were detected with MRI-targeted biopsy compared to TRUS guided biopsy.[7,39,40] Results of cognitive fusion studies are contrasting, as some studies show superior and others show inferior detection rates compared to TRUS guided biopsy, though, software assisted fusion seems not to be superior to cognitive fusion.[41-43]

The results of our review are in line with other studies showing that software assisted MRI-TRUS fusion guided biopsy detects more csPCa without increasing the detection of insignificant PCa.[4,34] The best biopsy strategy for PCa would only detect csPCa and no clinically insignificant PCa. The crux however is the definition of csPCa as no uniform definition exists.[44,45] The included studies in this review used seven different definitions of csPCa, with Gleason score ≥ 3+4 being most used. Furthermore, almost all included studies applied the same definition for csPCa for both targeted and systematic biopsy. The definitions of clinically significance however are based on systematic TRUS guided biopsy instead of targeted biopsy. As targeted biopsy obtains a few cores from an identified lesion on mpMRI which is likely to be PCa, it is much easier for targeted biopsy to fulfill the criteria for clinically significance compared to systematic TRUS biopsy. Ideally whole-mount sections of prostatectomy would be used as reference to draw the conclusion that targeted biopsy would detect more csPCa than systematic TRUS guided biopsy.

A difference in accuracy between direct in-bore biopsy and MRI-TRUS fusion is not yet demonstrated. Arsov et al.[17] concluded after a prospective randomized controlled trial that MRI-TRUS fusion combined with systematic TRUS-guided biopsy did not improve the PCa detection rate compared to direct in-bore guided biopsy in patients with at least one previously negative TRUS guided biopsy. To our knowledge, a study comparing direct in-bore guided biopsy with MRI-TRUS fusion alone is not yet performed. The cost-effectiveness of both direct in-bore and fusion guided biopsy is not yet proven definitely as presented evidence regarding the cost-effectiveness is contradictory.[46,47] Though, the procedure of MRI-TRUS fusion guided biopsy is less expensive, less time-consuming and more readily available than direct in-bore guided biopsy and therefore there might be an important role of MRI-TRUS fusion guided biopsy in the diagnostics of csPCa.

MRI-TRUS fusion guided biopsy is offered by several commercially available fusion platforms. No clear advantage is demonstrated of one platform over another.[13] One study was included in our review comparing the two software assisted image registration techniques.[9] They found a difference in favor of elastic registration. Though, the difference was not significant. This systematic review did not identify such a difference As a result of this review, costs and usability should be directive in the choice whether to use elastic or rigid registration.

The most important strength of this study is that it is the first to investigate the difference between elastic and rigid image registration used for MRI-TRUS fusion guided biopsy. A second important strength of this study is the calculation of OR between the detection of PCa by targeted biopsy compared to systematic biopsy. Bias introduced by a higher prevalence of prostate cancer in one group over another is hereby tried to exclude. This can be seen by the higher median detection rate for targeted biopsy in the elastic image registration subgroup compared to the rigid registration subgroup. As the detection rate for TRUS guided biopsy is also higher for that subgroup the OR between both subgroups does not significantly differ. Not all bias however can be excluded. Also a strength of this review is its focus on only studies assessing detection rates of targeted biopsy and systematic biopsy both in the same patient, in this way we attempted to reduce heterogeneity between studies. However, many included studies lack to mention the awareness of the operator of TRUS-guided biopsy of the identified lesion on mpMRI. This resulted in a poor outcome of the quality assessment of included studies. As a result the detection rate for TRUS guided biopsy might be overestimated.

A major limitation of this study is the heterogeneity between the included studies. Different definitions of csPCa, biopsy thresholds, and mpMRI protocols and scoring systems were used. Furthermore, significant heterogeneity can be introduced as there is a variation in non-rigid registration. The platforms use different in-house developed software. Also some heterogeneity is introduced as some patients had a TRUS biopsy before while others were biopsy naïve. More homogeneity can be achieved by using the START recommendations published by Moore et al.[48] Another limitation is the exclusion in some studies of patients without a lesion seen on mpMRI. This results in a selection bias probably in favor of targeted biopsy. A recurrent limitation in prostate biopsy studies is the impossibility of estimating the rate of true negative results of prostate biopsy. Studies are using TRUS guided biopsy as a reference test. This test however lacks accuracy. Studies using prostatectomy as gold standard are also biased as the study population consists of patients with PCa which needs surgery. As both analyzed subgroups suffer this limitation it will not affect the comparison between these subgroups. A last limitation might be the fact that the elastic image registration subgroup only exists of two different platforms while the rigid subgroup exists of eight different platforms.

To conclude, we did not identify a significant difference between rigid and elastic image registration for MRI-TRUS fusion guided biopsy in the detection of csPCa while both MRI-TRUS fusion guided biopsy techniques detect more csPCa than TRUS-guided biopsy. However, to address the aim of this review more appropriately, a study that compares elastic and rigid image registration more directly will be needed. Hereby, heterogeneity between both groups can be excluded.

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7

Cost-effectiveness comparison of imaging-guided prostate biopsy techniques: Systematic transrectal ultrasound, direct in-bore MRI and image fusion

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Abstract

Background Three commonly used prostate biopsy approaches includes systematic transrectal ultrasound (TRUS), direct in-bore magnetic resonance imaging (MRGB) and MRI-TRUS fusion guided biopsy. The aim of this study was to calculate which strategy is most cost-effective.

Materials and Methods A decision tree and Markov model were developed to compare cost-effectiveness. Literature review and expert opinion were used as input. A strategy was deemed cost-effective if the costs of gaining one quality-adjusted life year (incremental cost-effectiveness ratio) did not exceed the used willingness-to-pay (WTP) threshold of €80.000. A base case analysis was performed to compare TRUS and MRI-TRUS fusion guided biopsy. Because of a lack of appropriate literature regarding the accuracy of MRGB, a threshold analysis for MRGB was performed.

Results The incremental cost-effectiveness ratio for MRI-TRUS fusion biopsy compared with transrectal ultrasound guided biposy is €1386 per quality adjusted life year gained, which was below the WTP threshold and thus assumed cost-effective. If MRI is positive in a patient with csPCa, the sensitivity of MRGB for csPCa has to be at least 89% for csPCa, assuming an equal accuracy to MRI-TRUS fusion biopsy for insignificant PCa. If that is the case, the ICER is €80 000 per QALY gained and thus cost-effective.

Conclusion MRI-TRUS fusion seems to be cost-effective compared to TRUS guided biopsy. Future research is needed to provide evidence whether MRGB is the best pathway; in this study a threshold was calculated at which it would be cost-effective.

Introduction

Much progress has been made in the diagnosis of clinically significant prostate cancer (csPCa) with a growing role for multiparametric magnetic resonance imaging (mpMRI) in the last years.[1, 2] Despite expanding evidence on the superiority of mpMRI and targeted biopsy over 10-12 core transrectal ultrasound (TRUS) guided biopsy in the detection of csPCa, TRUS guided biopsy is still standard of care.[3-5] MpMRI is recommended if clinical suspicion of csPCa persists in spite of a negative TRUS guided prostate biopsy.[5]

Advantages of mpMRI and targeted biopsy are clear; in several men biopsy can be avoided and fewer but more accurate cores can be obtained.[6] However, a drawback could be the associated costs. Therefore, techniques have been explored such as MRI-TRUS fusion guided biopsy so that costs of direct in-bore targeted biopsy (MRGB) can be saved. MRI-TRUS fusion uses mpMRI images which are fused with real-time ultrasound images. Yet, the superiority of one targeted biopsy technique over the other is not established, however it is hypothesized that MRGB is more accurate compared to MRI-TRUS fusion guided biopsy.[7] As MRI-TRUS fusion guided biopsy still requires mpMRI, the technique is more expensive compared to conventional TRUS guided biopsy.

Although the procedure of targeted biopsy is more expensive, costs may be saved as less men will be over- and undertreated.[8] As a consequence, saving costs related to the therapeutic consequences may outweigh the higher diagnostic costs. Also, survival and quality of life (QoL) are affected by an accurate diagnosis which will influence the cost-effectiveness of the different biopsy strategies. However, testing such hypotheses in reality can be complex. To overcome these challenges, decision models are used.

Results of several decision models evaluating mpMRI and subsequent targeted biopsy are published already. [9-11] However, none of these studies evaluated the cost-effectiveness of MRGB, MRI-TRUS fusion guided biopsy and TRUS guided biopsy in one model. Therefore, our study is focusing on the difference in cost-effectiveness between the three approaches.

Material and Methods

Population

The hypothetical population of this study consists of biopsy naïve patients with a suspicion of having csPCa based on an elevated serum PSA or abnormal digital rectal examination (DRE).

Decision model

A decision-analytic Markov model was developed to compare the cost-effectiveness of two new diagnostic pathways with the current standard of care for detecting csPCa. A decision tree was made to model the three diagnostic pathways and subsequent treatment options (supplementary figure 1). The current standard of care is to perform systematic TRUS guided biopsy in patients with a suspicion of having csPCa. The first strategy we compared with this standard of care was the MRI-TRUS fusion pathway. In this pathway, elevated PSA or abnormal DRE is followed by mpMRI. In case a suspicious lesion is seen on mpMRI, an MRI-TRUS fusion guided biopsy is performed. The second strategy was MRGB. Here, MRI-TRUS fusion guided biopsy is replaced by MRGB. After biopsy, three options were available for patients: prostatectomy, radiotherapy (RTx) and active surveillance (AS). As focal treatment is not yet standard of care, we did not include this treatment in our model. We assumed that in patients with a false-negative test (mpMRI or biopsy) eventually PCa would be detected and that in patients with a false-insignificant test (biopsy) eventually csPCa would be detected.[12]

A Markov model was used to represent the follow-up. The Markov model consisted of different health states in which patients moved according to a set of transition probabilities. The health states were: status after prostatectomy, status after RTx, status after AS and dead. After each cycle (one year) patients could either stay in their health state or die, depending on the probabilities of that state. Costs and utilities were appointed to each health state. The time horizon for this analysis was 18 years, as the study we used to abstract the survival data from had a follow-up of 18 years.[13]

TreeAge Pro 2012 software (TreeAge Software Inc, Williamstown, MA, USA) was used for this analysis.

Transition probabilities

An overview of the used transition probabilities can be found in table 1. We assumed that the specificity of all three biopsy techniques for any PCa was 100% as a biopsy cannot be false positive. The remaining transition probabilities for TRUS guided biopsy and for MRI-TRUS fusion guided biopsy were subtracted from the "Comparison of Biopsy With Whole-Gland Pathology" data presented by Siddiqui et al.[4] The transition probabilities for mpMRI were derived from Abd-Alazeez et al.[14] considering Gleason ≥ 3+4 being csPCa. The distribution in initial treatment was based on our institutional situation.

Table 1 Transition probabilities used in the decision tree

Parameter	Value, %	Source
Tumor prevalence		
Tumor present when PSA is elevated (4-6 ng/ml)	25	Kranse [2008]
Tumor significant when a tumor is present[1]	50	Expert opinion
Treatment options		
Prostatectomy with csPCa[1]	70	Expert opinion[3]
Radiotherapy with csPCa[1]	25	Expert opinion[3]
Prostatectomy with insignificant tumor[1]	40	Expert opinion[3]
Radiotherapy with insignificant tumor[1]	10	Expert opinion[3]
mpMRI		
Sensitivity for csPCa[1]	93	Abd-Alazeez [2014]
Specificity for csPCa[1]	21	Abd-Alazeez [2014]
Specificity for any PCa	28	Abd-Alazeez [2014]
MRI-TRUS fusion		
Sensitivity for csPCa[2]	77	Siddiqui [2015]
False insignificant when mpMRI positive[2]	20	Siddiqui [2015]
Sensitivity for insignificant PCa[2]	50	Siddiqui [2015]
False significant when mpMRI positive[2]	32	Siddiqui [2015]
Specificity MRI-TRUS fusion guided biopsy any PCa	100	Expert opinion
TRUS		
Sensitivity for csPCa	53	Siddiqui [2015]
False insignificant	34	Siddiqui [2015]
Sensitivity for insignificant PCa	55	Siddiqui [2015]
False significant	34	Siddiqui [2015]
Specificity TRUS any PCa	100	Expert opinion
MRGB		
Specificity MRGB for any PCa	100	Expert opinion

1) csPCa is defined as Gleason score ≥ 3+4
2) csPCa is defined as GS ≥ high volume 3+4 (intermediate and high risk)
3) The distribution in initial treatment is based on our institutional situation.
PSA = prostate specific antigen; mpMRI = multiparametric magnetic resonance imaging; csPCa = clinically significant prostate cancer; TRUS = transrectal ultrasound; MRGB = direct in-bore magnetic resonance guided biopsy.

Cost information

Only health care costs were used in this cost analysis. Costs (€) were calculated according to the Dutch Methods for the economic evaluation of health care programs using costs information from the departments of Urology, Radiology, Radiotherapy and Pathology of our hospital.[15] An overview of the cost data used in this analysis is presented in table 2. Costs for prostatectomy were calculated by the weighted mean of open and robot-assisted laparoscopic (RALP) approach (50% each). We calculated costs for 3 days at the ward after prostatectomy and included it in the unit costs. Costs of pathology were included in all biopsy techniques and in the prostatectomy procedure. Also, the costs for urine incontinence (€638)[16] in the first year after prostatectomy and RTx were included in the unit costs, corrected by the probability for developing it (11,5 and 0% for prostatectomy and RTx respectively).[17] For the first year after RTx, costs for gastro-intestinal toxicity were included in the unit costs (Costs: €2545, probability: 7%).[18] We assumed no difference in chance of developing complications after the different biopsy

Table 2 Used cost data

Procedure	Unit costs[1], €
TRUS[2]	481
MRI-TRUS fusion	
mpMRI	317
Biopsy[2]	481
MRGB	
mpMRI	317
Biopsy	1095
Other costs	
Radiotherapy	8686
Radical prostatectomy	9415
Active surveillance/follow-up	100
Urine incontinence after year 1 for Radiotherapy	13
Urine incontinence after year 1 for prostatectomy	26

TRUS = transrectal ultrasound; MRGB = direct in-bore magnetic resonance guided biopsy; mpMRI = multi-parametric magnetic resonance imaging.

1) The costs of the different biopsy approaches includes purchase and maintenance. Also staff and material costs are included as is slot time (30 minutes for mpMRI, 60 for MRGB, 20 for TRUS and 20 for MRI-TRUS fusion).

2) Costs of MRI-TRUS fusion biopsy and TRUS biopsy were considered the same as the difference in purchase of an ultrasound machine with or without a fusion option is negligible. The additional costs of a fusion option would be around €3,- (+/- € 8.000,-, a lifetime of 5-7 years, +/- 400 patients per year).

procedures (0.8%)[19], the costs of complications after biopsy are based on 5 days at the ward (€2365). The costs for AS and for follow up after the two treatment options were considered to be equal. Costs of AS consist of one consults of an urologists and the measurement of PSA per year. All future costs were discounted to their present value by a rate of 4% according to the Dutch pharmacoeconomic guidelines.[20]

Outcome measures

Effectiveness was measured by health-related quality of life (QALY). QALYs are adjusted life years corrected by the quality of those adjusted years. Utilities[17] and survival data[13], obtained after systematically reviewing the literature, are presented in table 3. Natural survival data were obtained from Statistics Netherlands (CBS).[21] According to the Dutch pharmacoeconomic guidelines, effects were discounted with a rate of 1.5%.[20]

Data analysis

Mean costs, mean effects (in QALYs) and incremental cost-effectiveness ratios (ICERs) were calculated and compared between the strategies. ICERs are calculated by dividing the additional costs of a strategy by the additional QALYs as compared to another strategy. ICERs represent the additional costs to gain a QALY. The cost-effectiveness of a biopsy strategy is dependent on the willingness-to-pay (WTP) for one QALY. We used a WTP threshold of €80.000 (±£68.000 or $90.000) as recommended by the Dutch Council for Public Health and Care.[22] So, a strategy is deemed cost-effective if the costs of gaining one QALY is €80.000,- or less. Which is higher, for example, than the WTP threshold recommended by United Kingdom's National Institute for Health and Clinical Excellence (NICE) (£20.000 – 30.000; ± €24.000 – 36.000; $26.000 – 39.000).[23]

A base case analysis was performed between TRUS and MRI-TRUS fusion biopsy. Because of a lack of appropriate literature regarding the diagnostic accuracy of MRGB, a threshold analysis for MRGB was performed. We assumed an equal accuracy for both strategies for detecting insignificant PCa.

Table 3 Utilities and survival of different health states used in the Markov-model

Parameter	Value, %	Source
Utilities		
Biopsy	99.4	Heijnsdijk [2012]
PCa diagnosis	98	Heijnsdijk [2012]
Prostatectomy	75	Heijnsdijk [2012]
Radiotherapy	77	Heijnsdijk [2012]
Active surveillance	97	Heijnsdijk [2012]
Post recovery	95	Heijnsdijk [2012]
Survival		
Active surveillance for insignificant PCa	99.2	Bill-Axelson [2014]
Treated insignificant PCa	99.4	Bill-Axelson [2014]
Missed csPCa	97.4	Bill-Axelson [2014]
Treated csPCa	98.6	Bill-Axelson [2014]
Natural survival from the age of 65 (Year)		Statistics Netherlands [2014]
1	98.85	
2	98.7	
3	98.52	
4	98.31	
5	98.18	
6	98.02	
7	97.82	
8	97.63	
9	97.31	
10	97.06	
11	96.66	
12	96.22	
13	95.85	
14	95.17	
15	94.47	
16	93.91	
17	93.03	
18	92.32	

csPCa = clinically significant prostate cancer

Results

Cost-effectiveness of MRI-TRUS fusion compared to TRUS

According to our model, MRI-TRUS fusion is more effective compared to TRUS with an incremental effect of 0.13 QALYs. However, the latter procedure is less expensive with on average €2596 in costs per patient while the average costs of MRI-TRUS fusion per patient is €2771, which results in an incremental cost of €175 for MRI-TRUS fusion guided biopsy. As a result, the ICER for MRI-TRUS fusion guided biopsy is €1386 per QALY gained. As we assumed a WTP threshold of €80 0000, MRI-TRUS fusion is deemed cost-effective (table 4). Applying the threshold which is used by NICE, MRI-TRUS fusion would still be cost-effective.

Table 4 Baseline results of TRUS and MRI-TRUS fusion.

Strategy	Costs (€)	Effects (QALY)	Incremental costs (€)	Incremental effects (QALY)	ICER (€/QALY)
TRUS	2596	12.8162	x	x	x
MRI-TRUS fusion	2771	12.9425	175	0.1263	1386

TRUS = Transrectal ultrasound; MRI = magnetic resonance imaging; MRGB = direct in-bore magnetic resonance guided biopsy; QALY = quality-adjusted life year; ICER = incremental cost-effectiveness ratio.

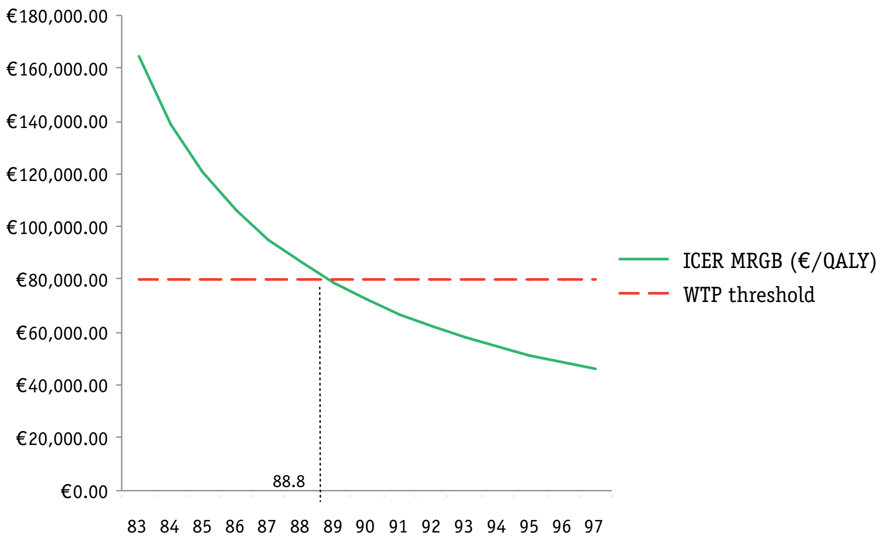
Threshold analysis for MRGB

MRGB would be cost-effective if the sensitivity for csPCa of MRGB is 11.8% higher than the sensitivity of MRI-TRUS fusion. So, if mpMRI is positive in a patient with csPCa, MRGB has to be true significant in at least 88.8% (77+11.8). If that is the case, the ICER is €80 000 per QALY gained and thus cost-effective (figure 1). In the hypothetical situation that the sensitivity of MRGB would be 100%, a gained QALY would cost €34 485 (ICER), this would just remain within the range recommended by NICE. The sensitivity of MRGB has to be 99% to be cost-effective, using the upper limit of the WTP threshold according to NICE. These calculations are based on the assumption that the sensitivity for insignificant PCa was the same for both biopsy techniques. Figure 2 is representing the results after varying this assumption.

Deterministic sensitivity analyses

We calculated in our base case analysis that MRI-TRUS fusion is cost-effective compared to TRUS with an ICER of €1386. Ranging the assumptions based on expert opinion, cost or diagnostic accuracy parameters with realistic variations did not change this outcome. For example, the assumption that a tumor is clinically significant in 50% of the cases that a tumor is present has to be 5% or less, so that

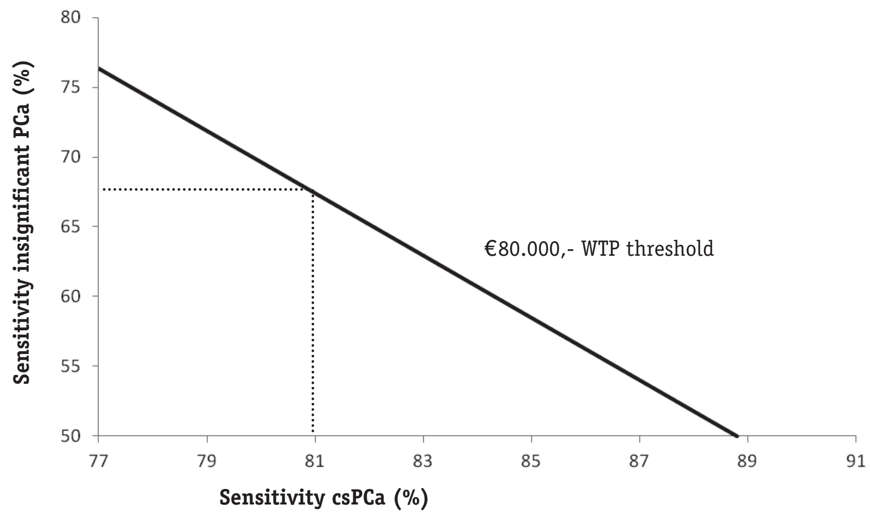
Figure 1 Incremental cost-effectiveness ratio (ICER) of direct in-bore magnetic resonance guided biopsy (MRGB)



On the x-axis the sensitivity of MRGB for clinically significant prostate cancer. On the y-axis the ICER in €/QALY. We assumed an equal accuracy for MRGB and MRI-TRUS fusion for detecting insignificant PCa. The dotted line is the willingness-to-pay (WTP) threshold of € 80.000. The ICER of MRGB is beneath the WTP threshold from an accuracy of 88.8%.

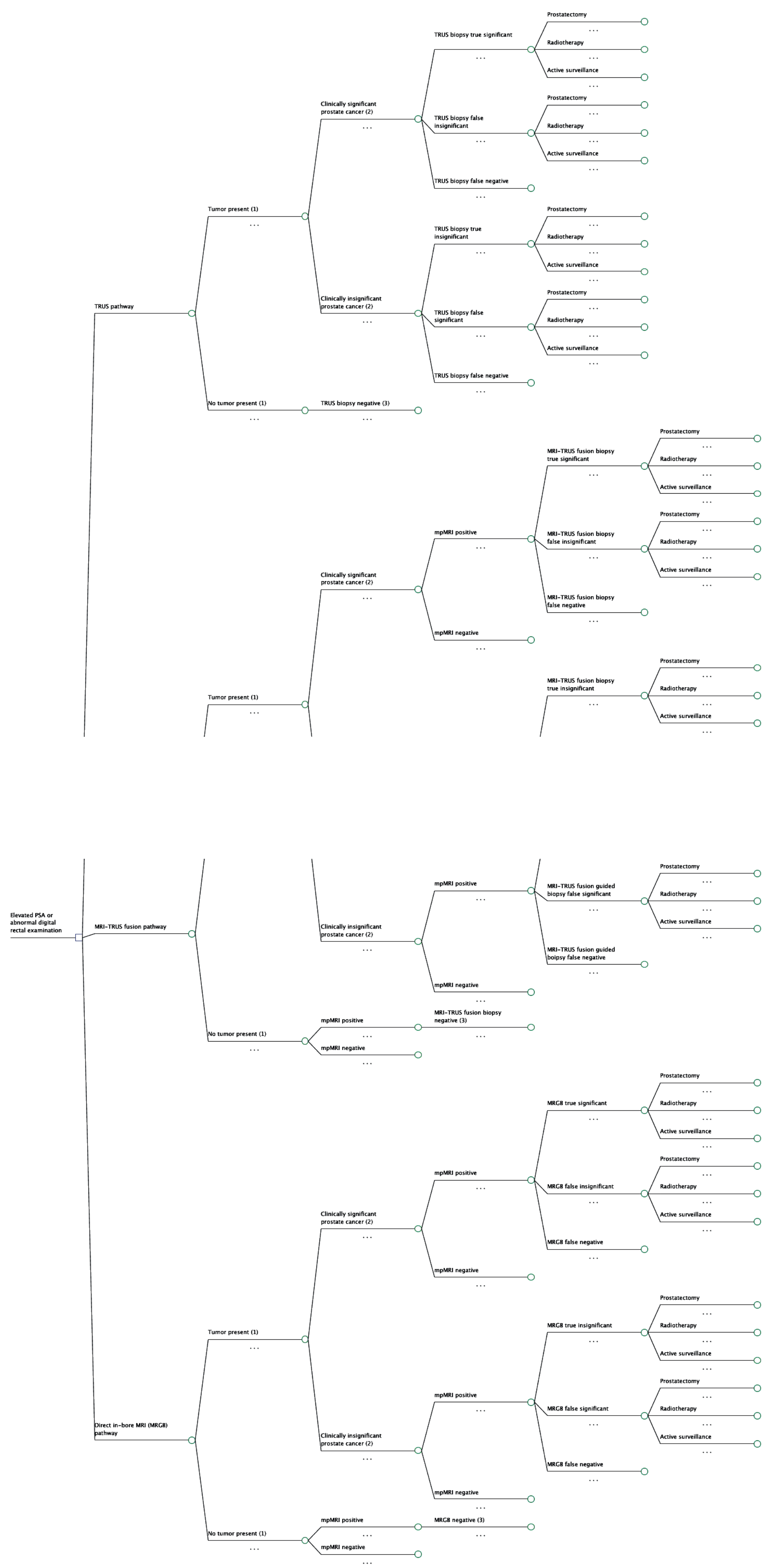
the TRUS biopsy pathway would become cost-effective, i.e. an incidence of csPCa of 1% in patients with raised PSA. Furthermore, the ICER of MRI-TRUS fusion would exceed the WTP threshold in case an mpMRI costs €9.500 or more per patient. The cost-effectiveness of MRI-TRUS fusion biopsy would be even higher with an increasing specificity of mpMRI for csPCa. For instance, a specificity of 80% (instead of 21%) would result in an ICER of €470. Varying utilities did not significantly change the outcome of our base case analysis. The parameters which were most sensitive to change the base case analysis were survival after a treated csPCa and the survival with an untreated clinically insignificant PCa. When the yearly survival of a patient with a treated csPCa lowers from 98.6% to 93.2% TRUS biopsy would be the most cost-effective strategy. This would also be the case if survival of an untreated insignificant PCa would decrease from 99.2% to 96.5%.

Figure 2 Analysis of the cost-effectiveness of direct in-bore magnetic resonance imaging guided biopsy (MRGB) varying the sensitivity for significant prostate cancer (PCa) of MRGB plotted over the sensitivity for insignificant PCa of MRGB



On the x-axis the sensitivity of MRGB for significant tumors. On the y-axis the sensitivity of MRGB for insignificant tumors. The black line is representing the willingness-to-pay (WTP) threshold of € 80.000. To illustrate, the dotted lines indicate that in case the sensitivity for csPCa of MRGB is 81%, the sensitivity of MRGB for insignificant PCa has to be 67.5% to reach the WTP threshold and thus to be cost-effective.

Supplementary figure 1 Decision tree representing the three evaluated pathways



Based on the used transition probabilities a hypothetical cohort of patients run through the model so that we could evaluate the consequences of the model and the transition probabilities.
(1) Regardless of the biopsy pathway, in every men, prostate cancer is present or not present.
(2) In case prostate cancer is present, it is always clinically significant or clinically insignificant.
(3) In case prostate cancer is absent, biopsy can never be positive. However, MRI can be false positive.

Discussion

The results presented in our paper indicate MRI-TRUS fusion to be cost-effective compared to TRUS guided biopsy. In case the sensitivity of MRGB for csPCa is at least 89%, MRGB is the most cost-effective strategy.

For several decades, healthcare expenditures has been growing rapidly. The rise in expenditures is based on multiple components with technological improvements, often used during the diagnostic process, playing an important role.[24] Also prostate cancer related costs are generated for a considerable part during diagnosis.[25] Our results suggest that, despite the fact that MRI-TRUS fusion guided biopsy increases the costs of the diagnostic process even more, MRI-TRUS fusion is the most cost-effective strategy as health benefits from an accurate diagnosis. In our hypothetical model, MRI-TRUS fusion and MRGB benefit from a high sensitivity of mpMRI and subsequently a high rate of true csPCa detection with biopsy and as a result, the targeted biopsy approaches increase survival as less patients are undertreated.

As the difference in initial costs between MRI-TRUS fusion and MRGB is €614 in favor of MRI-TRUS fusion, sensitivity of MRGB for significant disease has to be at least 89% to be the most cost-effective strategy. Previously, de Rooij et al.[9] developed a model to compare TRUS guided biopsy with MRGB. They suggested that MRGB is cost-effective assuming a sensitivity of MRGB of 90% for any PCa. Due to insufficient literature of MRGB accuracy data usable for our analysis, we decided to calculate a threshold for MRGB whereby using an important assumption could be avoided.

If specificity of mpMRI would increase, the cost-effectiveness of both targeted biopsy approaches would be better. Now, 72% of patients without any tumor and 79% of patients with an insignificant tumor wrongfully undergo biopsy and consequently make unnecessary costs and experience disutilities. Contradictory, a burden for targeted biopsy is the ability to sample the most aggressive part of a lesion seen on mpMRI. In 32% of the csPCa lesions detected with MRI-TRUS fusion guided biopsy, the lesion was downgraded after prostatectomy to insignificant PCa, thus incorrectly assessed as being significant[4]. As a consequence, additional costs are made and disutilities are experienced by falsely treating such patients. At this moment, definitions for clinically significance are based on studies using TRUS biopsy. As targeted biopsy is increasingly being practiced, new definitions should be used to overcome this paradoxical drawback.

An important strength of our study is the use of recently published studies which covered the performance of mpMRI, TRUS and MRI-TRUS fusion guided biopsy. To avoid misleading conclusions around MRGB we performed a threshold analysis. Further, we extensively explored the effects of the parameters based on expert opinion with sensitivity analyses. Willis et al.[10] concluded after a review of economic evaluations of diagnostic strategies for prostate cancer that the effect of difference in impact of prostate cancer and its treatment on the length and quality of life is rarely highlighted in studies regarding cost-effectiveness. Therefore, we also performed a comprehensive evaluation of the effect of the utilities and the survival.

Besides the strengths, we also have to discuss some potential limitations. The presented calculation is based on Dutch cost data. Therefore, it may be hard to extrapolate the model to other healthcare systems. We tried to overcome this limitation by presenting detailed input parameters. Hereby, the transferability of the results to another specific healthcare system can be assessed.[26] In addition, we provided the WTP threshold recommended by NICE, which applies a threshold lower than the Dutch Council for Public Health and Care does. The cost-effectiveness of MRI-TRUS fusion would not be influenced by this lower WTP threshold. However, lowering the threshold to the upper limit according to NICE, the sensitivity of MRGB for csPCa has to be 99% instead of 89% to be the most cost-effective approach. Another limitation is that it was inevitable to use parameters based on expert opinion. The parameters based on expert opinion are representing the actual situation in our hospital. Again, questions may rise about the generalisability to other countries. Though, sensitivity analyses showed that varying those assumptions with realistic variations did not change the outcome of the results. For example, the main parameter based on expert opinion is the assumption that a tumor is significant in 50% of the cases in which a tumor is present in men with raised PSA. However, varying this assumption with realistic values did not change the outcome of our analyses. Also, the distribution of treatments between patients was based on the experiences in our hospital. Again, varying this assumption did not affect the conclusion of our analyses. A last important assumption we have to address is the assumption that in patients with a false-negative test eventually PCa would be detected and that in patients with a false-insignificant test eventually csPCa would be detected. Due to its high false-negative rate and its high false-insignificant rate, the TRUS biopsy approach benefit most as survival increases in that group due to this assumption. Another limitation to keep in mind is the fact that this evaluation largely depends on the results of the included studies. All included studies suffer from a lack of a reliable gold standard to evaluate the performance of mpMRI, TRUS and MRI-TRUS fusion. We obtained the biopsy data published by Siddiqui et al.[4] A limitation of that study was that they excluded patients without a lesion seen on mpMRI. Therefore, accuracy of targeted biopsy might be overestimated. However, the negative predictive value of mpMRI is approximately 90%.[27] Thus, it is unlikely that this limitation would have changed the outcome of our analysis. Furthermore, to confine the consequences of the limitations we used a conservative modeling approach. The choices we made favored the TRUS biopsy pathway instead of the pathway regarding the new technologies. As all decision models encounter difficulties to represent actual complex situations, our model is hereby complicated. The results depend on the used input parameters as well as the depth of the calculation. For example, in our hospital mpMRI, MRGB and MRI-TRUS fusion biopsy is offered on a general basis and we therefore did not take into account costs coming with the introduction of the new technologies. Further, the cost-effectiveness of MRI-TRUS fusion and MRGB both depend on a high quality MRI. Unfortunately, in many countries sufficient prostate MR-quality is not warranted.

Conclusion

Taking the limitations in consideration, MRI-TRUS fusion seems to be more cost-effective compared to TRUS guided biopsy in a Dutch healthcare setting. Future research is needed to provide evidence whether MRGB is cost-effective as we calculated a threshold from where MRGB would be cost-effective.

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Discussion

Discussion

mpMRI

As discussed in the introduction, the advantages of mpMRI and targeted biopsy are clear: in some men biopsy can be avoided and fewer but more accurate biopsy cores can be obtained. As the chance of developing complications after a prostate biopsy is almost 1%, avoiding biopsy will reduce patient burden substantially.[1] With a known sensitivity of 93% (95% CI, 88-96) and a negative predictive value of 89% (95% CI, 83-94), men with negative mpMRI results might safely avoid biopsy.[2] Nowadays, several institutions worldwide are using mpMRI to detect or to rule out csPCa. In the introduction we discussed the lack of literature about which proportion of patients avoids biopsy in a daily clinical routine because of negative findings on mpMRI. In *Chapter 2* we demonstrated that 59.4% of men had such negative mpMRI results and thus avoided unnecessary biopsy. These results are remarkably higher compared to findings by other research groups.[2,3] Recently, the PROMIS trial and the PRECISION trial reported that approximately 30% of patients avoid biopsy by using mpMRI as triage test.[4] An explanation may be that our institution is experienced in mpMRI of the prostate. This is probably the explanation of our results being higher compared to other presented results. Another explanation is that PI-RADS may be applied conservatively in the afore mentioned studies, so as not to miss any significant tumors. This may introduce a bias, which is not present in the routinely scored exams of our retrospective study. This is also seen in the relatively large group of patients with a PI-RADS 3 in those trials. Also, an explanation may be that in a part of our patients with a PI-RADS 1 or 2 lesion was false negative.

The differences between our and other presented results underlines the importance of adequate training in prostate MRI so that in daily clinical practice high sensitivities and negative predictive values can be obtained. If that can be achieved, then almost 60% of men can safely avoid biopsy according to our findings. The major challenge now is to take care every institute implementing mpMRI achieves acceptable sensitivities and specificities. The skills required for obtaining images with a good quality and the skills required for reading and interpreting are quite hard to train. Therefore, there are continued attempts to educate and train readers to provide uniform results worldwide.

In *Chapter 3* we showed that in patients with mpMRI lesions classified PI-RADS 3, 4 or 5 csPCa were detected in 17%, 34% and 67% respectively with MRGB.[5] Similar detection rates are found by other research groups.[2,6-9] These numbers implicates that there is some work to do in order to increase the detection rates for csPCa, especially in PI-RADS 4 and 5. As PI-RADS 3 is reserved for those lesions which cannot be classified otherwise, the number of lesions scored PI-RADS 3 should be as low as possible. PI-RADS version 2, published in 2016, supports radiologists to avoid a PI-RADS 3 score as much as possible by upgrading a lesion to PI-RADS 4 in case DCE is positive in lesions in the peripheral zone of the prostate classified PI-RADS 3 on DWI. Furthermore, lesions located in the transition zone classified PI-RADS 3 on T2-weighted imaging can be upgraded to PI-RADS 4 in case DWI is scored 5.[10] In addition to this, we now demonstrated in *Chapter 3* that lesions overall classified PI-RADS 3 can be downgraded by using the PSA density. In 0-9% of men with lesions scored PI-RADS 3 and a PSA density below 0.12 ng/ml/ml csPCa is detected. This implies that a PI-RADS 3 lesion with a low PSA density can be downgraded to PI-RADS 2. As a consequence, such a patient avoids prostate biopsy. These findings are supported by findings presented by other research groups. For example, Hansen et al. showed a negative predictive value of 91% in patients with lesions scored PI-RADS 1 or 2 in combination with a PSA density below 0.1 ng/ml/ml. As a consequence, 8% of their study population could safely avoid biopsy.[11] In our population, 26% of patients with a PI-RADS 3 could have been downgraded to a PI-RADS 2. This could be increased to 42% by using a PSA density threshold of 0.15 ng/ml/ml. With this threshold, in 2-15% of patients with PI-RADS 3, csPCa would then be missed. By additionally using a PSA density thresholds, patient burden and costs could be saved. However, we will then have to accept a small proportion of false negatives.

MRI-targeted prostate biopsy

In *Chapter 3* we demonstrated the results of MRI-targeted biopsy in patients with suspicious lesions. The used biopsy method was direct in-bore targeted (MRGB). This procedure, however, needs to be performed in a separate session because image post-processing and tumor detection and localization demand time. Therefore, the procedure is not readily implemented in daily clinical practice. The procedure is time consuming and it costs MRI “slot-time” which is scarce worldwide. Nonetheless, direct in-bore biopsy seems to be the most accurate way to target a suspicious mpMRI lesion.[12] Although, in *Chapter 4* we did not demonstrate significant differences between FGB and MRGB.[13] Though, a major limitation of the study described in that chapter was the retrospective study design with a relatively small sample size. This is clearly illustrated by the wide range of 95% confidence intervals for FGB. This limitation could be a good explanation for the fact that we did not detect significant differences between both targeted biopsy methods. Unfortunately, there still is a great lack of literature addressing any differences in accuracy between different MRI-targeted biopsy methods.[12,14] However, the question is whether relatively small differences between the MRI-targeted biopsy methods really matters. Given the limited availability of MRI “slot-time” it is not likely that MRGB will be widely accepted as primary targeted biopsy strategy. It is more likely that MRGB will be a solution in selected cases, for example small lesions or lesions located ventrally or in the apex of the prostate or in patients with an PI-RADS (3), 4 or 5 and (repetitive) negative FGB sessions.

Negative targeted biopsy results

Of special interest for future studies are patients with positive findings on mpMRI and yet negative targeted biopsy findings. As targeted biopsy in mpMRI suspicious lesions is increasingly being practiced, urologists more often are faced with patients with a suspicious lesion detected on mpMRI but a negative pathology outcome for that lesion. Previously, Chelluri et al. performed a study to determine the yield of repeated FGB of a same lesion in patients having a prior negative FGB.[15] Repeated FGB in such lesions resulted in 6% csPCa detection. They concluded that negative FGB findings despite a positive mpMRI finding is a reliable finding. Though, our conclusion in *Chapter 5* is the opposite. We reproduced their study, now repeating MRGB of a same lesion in patients having prior negative MRGB. The yield of csPCa in repeated MRGB was 21%. We thus concluded that patients might benefit from an MRGB in a positive mpMRI lesion despite a prior negative MRGB. As repeated MRGB is not regularly performed, we had to include all patients from 2006 untill 2016. As a consequence, our sample size was quite small and this potentially limited our study. More literature, and prospectively collected data, is needed to determine the implication of a negative targeted biopsy finding (be it MRGB or FGB) despite a positive mpMRI finding. This is relevant as in this clinical scenario, patients are often intensively followed by measuring PSA, repeating mpMRI and even repeating targeted biopsy. During the data collection for some parts of this thesis, we encountered some patients who have had over 10 mpMRI sessions within the last 10 years. In future, we need to evaluate whether such an intensive follow up is needed.

Another study that will be submitted for publication soon, in which we cooperated with a research group from Switzerland, evaluates the utility of MRGB in the same lesion with negative prior FGB despite positive mpMRI lesions. In 25% (n = 14/56) of such lesions, csPCa was detected with MRGB.

Also, in *Chapter 3* we performed an evaluation to investigate whether patients with negative biopsy findings yet positive mpMRI findings are being diagnosed with csPCa after our study period. With a median period of 41 months, this follow up was too short to make firm conclusions.

Role of ultrasound

As already mentioned, despite MRGB seems to be the most accurate targeted biopsy approach, FGB will have an important role in the diagnosis of csPCa in patients with positive mpMRI findings as it is a technique which is relatively simple and cheap to implement in a urologist’s practice. Several commercially available platforms worldwide are now offering software to fuse mpMRI with TRUS. There are a lot of differences between the various platforms. For example, the use of tracking mechanism (mechanical arm or electromagnetic), biopsy route (transrectal or transperineal) or the way images are displayed (side-by-side or superimposed). The main difference between the platforms, however, is in the way of image registration: rigid or non-rigid (elastic). Rigid registration does not compensate for possible prostate deformation due to, for example, the introduction of an ultrasound probe while elastic image registration uses software to register the prostate deformation and artificially modifies the mpMRI images. Hereby, mpMRI data is stretched and distorted so that a reliable overlay is achieved.[16] In *Chapter 6* we demonstrated that there is no significant difference between rigid and non-rigid image registration.[17] A previously published study comparing the different fusion platforms also did not detect differences in detection rates for csPCa.[18] Our results may be explained by the fact that rigid image registration requires a cognitive optimization after the image registration is done. Further, we confirmed findings by other research groups that FGB detects more csPCa compared to TRUS biopsy.[2,8,12,19,20] As evidence is thickening about the superiority of mpMRI and targeted biopsy over TRUS biopsy we have to reevaluate the value of TRUS biopsy in the diagnostic process. Nowadays, most groups demonstrating superiority of MRI-targeted biopsy over TRUS biopsy conclude that a targeted approach might benefit patients with prior negative TRUS biopsy or they conclude that MRI-targeted biopsy may be beneficial as an additional approach next to TRUS biopsy. This is supported by csPCa detection with a TRUS biopsy approach in men with negative mpMRI findings or negative MRI-targeted biopsy results.[2,8] Most authors nowadays propose a targeted biopsy approach in addition to systematic TRUS-biopsy. However, you might argue the relevance of csPCa detection by TRUS in cases without lesions seen on mpMRI. It is questionable whether such a finding does affect a men his life. Interesting is the way the PROMIS trial handles positive TRUS findings with negative findings on template biopsy. Their statistical analysis plan treated such findings as false positives.[2] Nowadays, the definitions of csPCa are based on TRUS studies. With targeted biopsies performed, we should reevaluate whether old csPCa definitions are still relevant. With mpMRI and targeted biopsy now being performed, we are able to add mpMRI characteristics next to pathology characteristics to determine a lesion as being clinically significant, for example PSAD en ADC characteristics. In future, to omit TRUS biopsy will be one of the most important steps in PCa diagnostics, especially patients will be relieved to avoid TRUS biopsy. Hereto, we have to decrease the number of csPCa detected with TRUS while missed by mpMRI and/or subsequent MRI-targeted biopsy. Also, we probably have to accept a number of false negative findings in a targeted only approach.

Cost-effectiveness

A frequently heard argument against mpMRI and targeted biopsy is the increased initial costs of the diagnostic work-up. However, according to different cost-effectiveness studies, a targeted biopsy approach using an mpMRI defined target might be cost-effective.[21-23] In *Chapter 7* we concluded that a targeted biopsy approach using FGB indeed seems to be beneficial.[24] Although the initial costs of mpMRI and targeted biopsy exceed TRUS biopsy, mpMRI and targeted biopsy seems to be cost-effective as this last approach benefits health and quality of life; less men are under diagnosed so that an adequate treatment can be used. To test such hypothesis in reality is complex, therefore decision models are being used. Results from such studies, however, should be evaluated with caution. A major limitation is that all decision models encounter difficulties representing actual situations. Using a decision model forces you to make choices what to address and what not to address in your model. Also, during the design of the model, possibly not all situations are thought of. For example, a lot of patients with negative mpMRI findings are now often intensively followed by repeating PSA, mpMRI and sometimes even MRGB. This is a factor which is hard to implement in a decision model.

Future directions

To place mpMRI and targeted biopsy in a more prominent role in the diagnostic process of men suspected for having csPCa, possibly the most important issue to address is the follow up after 1) negative mpMRI findings, 2) positive mpMRI findings but negative targeted biopsy findings and 3) positive mpMRI findings but insignificant PCa with targeted biopsy. As a consequence of our limited knowledge of the above mentioned issues, often patients are now intensively being followed. PSA is most used for follow up. However, in an important amount of patients, mpMRI is repeated multiple times and sometimes MRGB is even being repeated several times.

Also, the role of ultrasound in follow up is not yet appropriately addressed. Research is still being performed to optimize ultrasound. For example, the use of various ultrasound modalities are being investigated. In response to multiparametric MRI, some use the term multiparametric ultrasound (mpUS).[25,26] A role for mpUS, maybe in the follow up of lesions localized with mpMRI, might further reduce costs.

Another important issue to address is the current definition of csPCa. In literature, different definitions are being used. Nowadays, most used is any Gleason score 3 + 4 finding. Despite the several different definitions being used, they all have one thing in common: they do not apply targeted biopsy. Survival studies are needed to determine the implication of biopsy findings using targeted biopsy. The implication of a Gleason score 3+4 detected by a targeted biopsy approach might be different from a same Gleason score detected by TRUS biopsy. Also, mpMRI should have a more important role in the determination of a lesion being csPCa. For example, lesion size and parameters such as PSA density, ADC values or enhancement patterns may be useful in the prediction of a lesion being csPCa or not. One or two biopsy samples from a lesion is probably not sufficient to predict whether a lesion will influence a men his life. Though, a downside for using lesion volume on mpMRI is the risk of both overestimation and underestimation of true tumor volume.[27-29] Nonetheless, we should evaluate its opportunities in long-term survival data. In my opinion mpMRI and targeted biopsy must have a more prominent role in nomograms as it probably improves csPCa prediction.

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Summary

The preceding chapters of this thesis addressed the role of MRI and MRI-targeted biopsy of the prostate. Both direct in-bore and MRI-TRUS fusion guided biopsy were addressed.

Approximately one out of six men will be diagnosed with PCa in his life. Luckily, most of those men will not die from the disease and their lives will not be affected. In some men, however, this will be the case; their lives will be affected or they will die from PCa. Those cancers are referred to as clinically significant PCa (csPCa).

The current standard to detect csPCa is to obtain prostate tissue with systematic 12-core transrectal ultrasound guided biopsy (TRUS biopsy). Unfortunately, this procedure has major drawbacks. Therefore, nowadays MRI and subsequent MRI-targeted biopsy is increasingly being practiced. Radiologists reading MRI of the prostate, will assign a lesion on a scale (PI-RADS scale) from 1 to 5. With a higher score, the chance of having csPCa is higher. After a lesion is detected and scored PI-RADS 3, 4 or 5, it will be biopsied. This can be done within the MRI scanner (MRGB) or after fusing MRI images with ultrasound images (FGB).

In *chapter 2* we demonstrated the distribution of PI-RADS in a population of men having mpMRI within the last six years. In this chapter, evaluating mpMRI in 4259 patients in our institution, it was shown that 59.4% could avoid prostate biopsy because there PI-RADS score was 1,2 or 3 with a prostate specific antigen blood level (PSA) density below 0.15 ng/ml/ml.

Chapter 3 reports on the experience of MRGB in our institution. We retrospectively included 1057 patients having MRGB in our institution. All included patients had a PI-RADS score ≥ 3. csPCa was detected in 17%, 34% and 67% in patients with PI-RADS 3, 4 or 5 respectively. We further demonstrated that PSA density could be used in patients with a PI-RADS 3 lesion to avoid biopsy. In case patients with a PI-RADS 3 lesion and a PSA density below 0.15 ng/ml/ml would not be biopsied, 42% of those men avoids biopsy. In 2 – 15% of men avoiding biopsy, csPCa would have been missed.

In *chapter 4* we performed a comparison of csPCa detection rates between FGB and MRGB. We included 51 patients with FGB and 227 patients with MRGB. All patients had a history of at least one prior negative TRUS biopsy and lesions scored PI-RADS 4 or 5 with a lesion size of at least 8 mm. The detection rate of csPCa for FGB was 49% compared to 61% for MRGB. This difference did not significantly differ.

Chapter 5 evaluated the yield of repeat MRGB after a first negative MRGB in a same lesion. Within a timeframe of ten years, 62 patients met the inclusion criteria. Together, they had 63 lesions which were resampled during second MRGB.

Two radiologists reassessed all MRI and MRGB images. In 21% of those lesions, csPCa was detected during repeat MRGB while first MRGB was negative for any PCa. In two patients, csPCa was detected at repeat biopsy while the volume of the lesion, determined on MRI, decreased. In none of the patients with a decreasing PSA between both MRGB sessions, csPCa was detected. Remarkable is the finding that 19% of lesions score PI-RADS 2 at first MRI proved to be csPCa after MRGB.

In *chapter 6* we performed a systematic review and meta-analysis to compare rigid and elastic image registration in FGB. After searching different electronic databases, 11 papers describing elastic and 10 papers describing rigid image registration were included for further analysis. The calculated odds ratio (OR) for detecting csPCa by using rigid image registration compared with TRUS biopsy was 1.4, the OR was 1.45 for elastic image registration. This did not significantly differ while both image registration techniques detected significantly more csPCa compared to TRUS biopsy.

Chapter 7 evaluated the cost-effectiveness of three approaches in the diagnostic work up of patients with a raised PSA level or a suspicious digital rectal examination. The aim of the study was to calculate whether TRUS biopsy, FGB or MRGB was the most cost-effective strategy. Therefore, a decision tree and Markov model was developed. Literature review and expert opinion was used as input for this model. Because of a lack of appropriate literature regarding the accuracy of MRGB, we performed a base case analysis to compare TRUS and FGB and we performed a threshold analysis for MRGB. The incremental cost effectiveness ratio for FGB compared with TRUS was €1386 per quality adjusted life year gained. This is below the willingness-to-pay- threshold of €80.000 and thus cost-effective. The sensitivity of MRGB has to be at least 88.8% to be cost-effective.

Finally, in *chapter 8* the role of MRI and subsequent targeted biopsy, both MRGB and FGB, was discussed. The main conclusion is to increase MRI reading quality by training radiologists. Future research is needed to determine the implication of negative MRI findings and negative biopsy findings as nowadays MRI and biopsy is repeated, this is probably unnecessary. Hereby, costs and patients discomfort can be avoided.

Samenvatting

In dit proefschrift werd de rol van MRI en MRI geleide prostaat biopsie onderzocht voor de diagnose van prostaatkanker. Twee methoden van MRI geleide prostaat biopsie werden hierbij bestudeerd, direct in de MRI scanner afgenomen biopsie (MRGB) en biopsie met behulp van echografie waarop eerder gemaakte MRI beelden worden gefuseerd (FGB).

Bij ongeveer 1 op de 6 mannen wordt in zijn leven prostaatkanker gediagnosticeerd. Een klein gedeelte van de mannen met prostaatkanker zal aan de ziekte overlijden of gaat er in zijn leven last van hebben. Een dergelijke prostaatkanker noemen wij klinisch significante prostaatkanker (csPCa).

De huidige manier om csPCa te detecteren, is door systematisch met behulp van een transrectale echografie 12 weefselbiopten te nemen (TRUS). Helaas zitten er grote nadelen aan deze procedure. Daarom wordt er tegenwoordig steeds meer gebruik gemaakt van MRI en MRI geleide biopsie. Radiologen die de MRI beelden van de prostaat beoordelen geven een score aan afwijkingen die zij detecteren. Deze score gaat van 1 tot 5 (PI-RADS score). Hoe hoger de score, hoe waarschijnlijker het is dat de afwijking csPCa betreft. Afwijkingen met een score van PI-RADS 3, 4 of 5 worden over het algemeen gebiopteerd. Dit kan gedaan worden via MRGB of FGB.

In *hoofdstuk 2* werd de verdeling van de PI-RADS score gedemonstreerd in een populatie van mannen die de afgelopen zes jaar een MRI van de prostaat in ons ziekenhuis hebben gehad. In dit hoofdstuk, waarbij de MRI scans van 4259 patiënten werden geëvalueerd, werd aangetoond dat 59.4% van de mannen prostaat biopsie konden voorkomen omdat hun PI-RADS score 1 of 2 was of een PI-RADS score van 3 met een prostaat specifiek antigeen (PSA) densiteit lager dan 0.15 ng/ml/ml.

Hoofdstuk 3 beschrijft de ervaring in ons ziekenhuis met MRGB. We hebben retrospectief 1057 patiënten geïncludeerd. Alle patiënten hadden een PI-RADS score groter of gelijk aan 3. csPCa werd gedetecteerd bij 17%, 34% en 67% van de patiënten met respectievelijk een PI-RADS score van 3, 4 of 5.

Verder werd gedemonstreerd dat de PSA densiteit gebruikt kon worden bij patiënten met een PI-RADS 3 score om biopsie te voorkomen. Als patiënten met een PI-RADS 3 en een PSA densiteit lager dan 0.15 ng/ml/ml geen biopsie ondergaan, hoeven 42% van de mannen met een PI-RADS 3 niet gebiopteerd te worden. Bij 2-15% van die mannen zal helaas csPCa gemist worden.

In *hoofdstuk 4* werd een vergelijking gemaakt in de detectie van csPCa tussen FGB en MRGB. We includeerden 51 patienten die FGB hebben ondergaan en 227 patienten die MRGB hebben ondergaan. Alle patiënten hebben in het verleden één of meerdere TRUS biopsie sessies ondergaan die negatief waren voor csPCa. Alle patiënten hadden afwijkingen die met MRI gescoord werden als PI-RADS 4 of 5. De afmetingen van de afwijking waren minstens 8 mm. Bij FGB werd in 49% van de mannen csPCa ontdekt, bij MRGB was dit 61%. Dit verschil was niet statistisch significant.

Hoofdstuk 5 evalueerde de detectie van csPCa in afwijkingen waarbij een eerder verrichte MRGB negatief was voor csPCa. In een tijdsbestek van tien jaar werden 62 patiënten geïncludeerd. Samen hadden zij 63 afwijkingen die tweemaal werden gebiopteerd waarbij de eerste biopsie negatief was. Twee radiologen herbeoordeelden alle MRI beelden en de beelden van de MRGB. In 21% van de afwijkingen die opnieuw gebiopteerd werden, werd csPCa ontdekt. Bij twee patiënten nam de omvang van de afwijking op MRI af terwijl er wel csPCa werd ontdekt bij de tweede MRGB. Bij geen enkele patiënt met een dalende PSA bloedwaarde werd csPCa ontdekt bij herhaalde MRGB. Opmerkelijk is het feit dat bij 19% van de afwijkingen die PI-RADS 2 scoorden, csPCa werd ontdekt bij de tweede MRGB sessie.

In *hoofdstuk 6* werd een systematische review en een meta-analyse verricht om rigide en elastische registratie te vergelijken bij FGB. Na verschillende elektronische databases te raadplegen werden 11 artikelen die elastische en 10 die rigide registratie toepasten, geïncludeerd. De berekende odds ratio (OR) voor het ontdekken van csPCa met rigide registratie vergeleken met TRUS biopsie was 1.4, de OR voor elastische registratie vergeleken met TRUS biopsie was 1.45. Dit verschil was niet statistisch significant. Beide registratie technieken detecteerden wel significant meer csPCa vergeleken met TRUS biopsie.

Hoofdstuk 7 evalueerde de kosten-effectiviteit van drie benaderingen om csPCa te detecteren bij mannen met een verhoogd PSA of een afwijkend rectaal toucher. Het doel van de studie was om de kosten-effectiviteit van TRUS biopsie, FGB en MRGB met elkaar te vergelijken.

Hiervoor werd een besliskundig model gemaakt. Gepubliceerde literatuur en de mening van experts werden gebruikt als input gegevens voor het model. Omdat er weinig literatuur is die kon gebruikt worden voor de input van MRGB, werd er voor MRGB een drempelanalyse verricht.

De verschillende strategieën zijn vergeleken op kosten, voor kwaliteit gecorrigeerde levensjaren (QALY's) en incrementele kosteneffectiviteitsratio's. De incrementele kosteneffectiviteitsratio laat zien wat het kost om een QALY te winnen ten opzichte van een andere strategie.

De incrementele kosten effectiviteitsratio voor FGB vergeleken met TRUS was €1386 per QALY. Dit bedrag is lager dan de drempelwaarde van €80.000 die veel gebruikt wordt om te bepalen of een strategie kosten effectief is.

De sensitiviteit van MRGB moet 88.8% zijn om de meest optimale strategie te zijn.

In *Hoofdstuk 8* werd ten slotte bediscussieerd wat de rol van MRI en MRI geleide prostaat biopsie is in de diagnostiek van prostaatkanker. De belangrijkste conclusie is dat de kwaliteit van de beoordeling van prostaat MRI in alle ziekenhuizen verhoogd moet worden door middel van training. Toekomstig onderzoek moet zich

vooral richten op de betekenis van negatieve bevindingen bij MRI of negatieve bevindingen bij MRI geleide biopsie. Nu wordt onderzoek vaak herhaald, vermoedelijk zonder dat dit relevant is. Hiermee worden onnodige kosten gemaakt en ervaren patiënten veel ongemak.

PhD Portfolio

Institute for Health Sciences
Radboudumc

Name PhD candidate:	**PhD period:**
W. Venderink	01-01-2015 – 11-12-2018
Department:	**Promotor(s):**
Radiology	Prof. J.J. Fütter and Prof. J.O. Barentsz
Graduate School:	**Co-promotor(s):**
RIHS	Dr. J.P.M. Sedelaar and Dr. Ir. H.J. Huisman

	Year(s)	ECTS
TRAINING ACTIVITIES		
a) **Courses & Workshops**		
- BROK course	2015	1,5
- Endnote	2015	0,5
- RIHS introduction course for PhD candidates	2015	1,0
- Introduction day Radboudumc	2015	0,5
b) **Seminars & lectures**		
- Radboud Research Rounds	2015	1,0
- Center for medical imaging- North Easth Netherlands conference	2015	0,25
c) **Symposia & congresses**		
- European Society of Urologycal Imaging (poster, Milan)	2016	0,5
- European Congres of Radiology (oral, Vienna)	2016	0,5
- RSNA (oral, Chicago)	2016	1,25
- Society of Computed Body tomography and MR (poster, Nashville)	2017	1,0
d) **Other**		
TEACHING ACTIVITIES		
e) **Lecturing**		
- Invited speaker 10th International Symposium on Focal Therapy and Imaging in Prostate and Kidney Cancer	2018	0,75
f) **Supervision of internships / other**		
- Supervision of research internship of two medical students	2016-2018	2,0
TOTAL		12,25

Radboud University Radboudumc
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List of publications

Venderink W, van Luijtelaar A, van der Leest M, Barentsz JO, Jenniskens SFM, Sedelaar JPM, Hulsbergen - van de Kaa CA, Overduin CG, Futterer JJ. Experience in 4259 men to avoid prostate biopsy by using multiparametric MRI and PI-RADS at an expert centre.
Submitted

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To be submitted

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Lieve Paulien, na al die jaren artikelen schrijven nu dan toch een "writers block". Op jouw dringend verzoek geen zoetsappig verhaal en vooral geen huwelijksaanzoek: Gewoon bedankt dan maar!

Curriculum Vitae

Wulphert Venderink is op 17 oktober 1988 geboren in Apeldoorn. Achtereenvolgens werden daar de peuterschool, de basisschool en ten slotte in 2007, aan het Christelijk Lyceum, het VWO met succes afgerond. Halverwege de opleiding geneeskunde werd de studie een jaar gepauzeerd om fulltime een bestuursfunctie te vervullen bij de studievereniging. Na dit korte intermezzo werd in 2015, met de afronding van zijn scriptie aan de Glasgow University in Schotland, de opleiding geneeskunde behaald (Radboud Universiteit). Twee jaar later werd de studie Nederlands recht aan de Radboud Universiteit afgerond. De scriptie voor de afstudeerrichting Straf- en Strafprocesrecht beschreef de juridische aspecten van postmortale radiologie. Op 1 januari 2015 begon het werkende leven met de start van een promotietraject op de afdeling Radiologie en Nucleaire Geneeskunde van het Radboudumc te Nijmegen. Het resultaat hiervan heeft u (als het goed is) inmiddels gelezen. Op 1 januari 2017 werd gestart met de opleiding tot radioloog op dezelfde afdeling.

Na zes jaar samenwonen in Nijmegen en een latrelatie van een jaar, wonen Wulphert en Paulien weer samen, nu in Deventer.

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